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CELL CYCLE AND CYCLE REGULATORS

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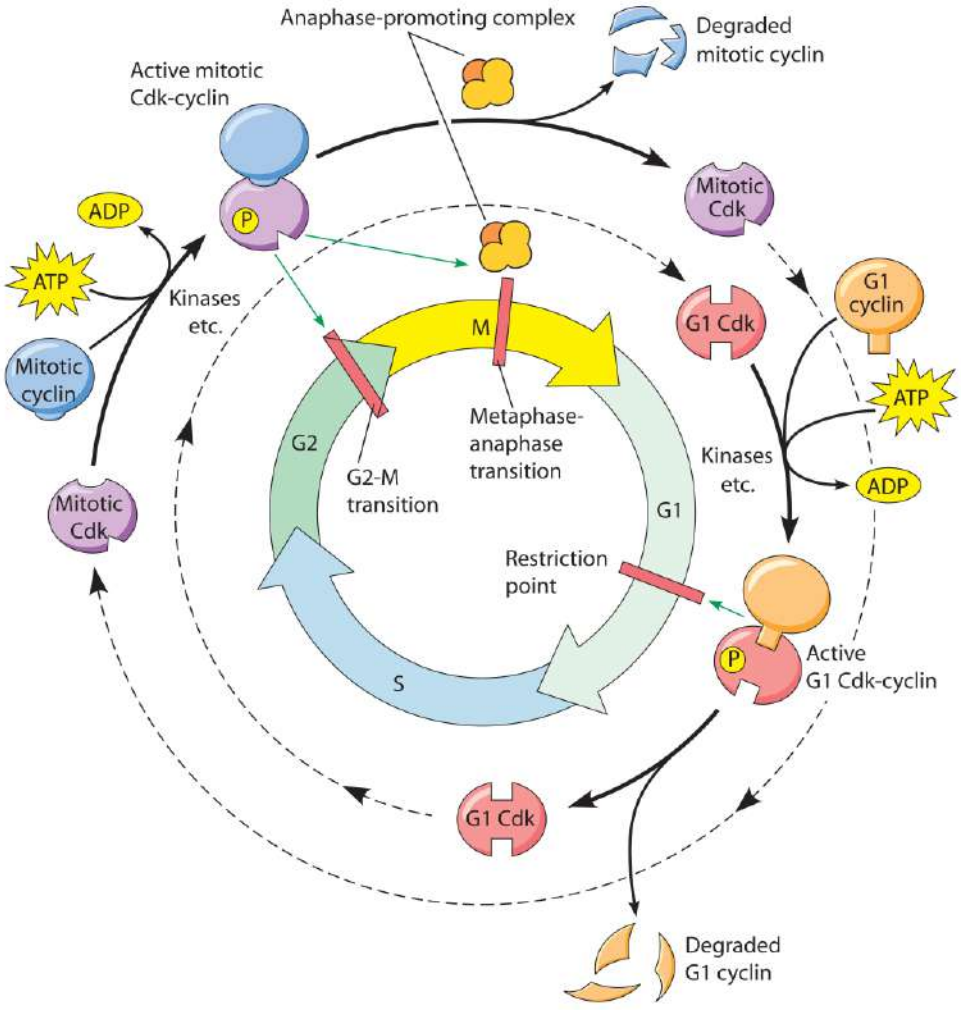
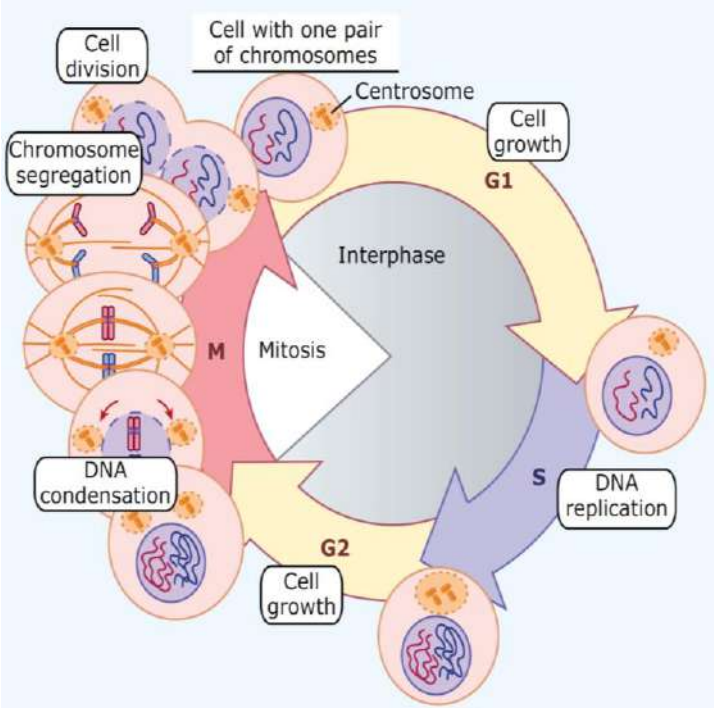
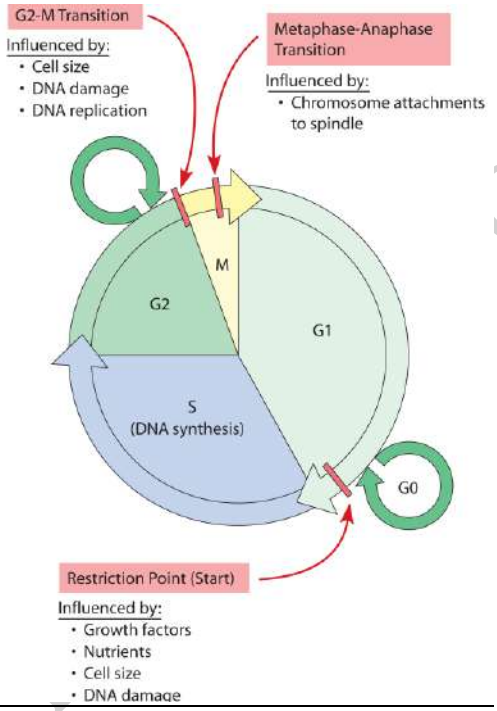


FIGURE 19-41 A General Model for Cell Cycle Regulation. Passage through the three main transition points in the cell cycle is triggered by protein complexes made of cyclin and Cdk, whose phosphorylation of other proteins induces progression through the cycle. G1 Cdk-cyclin acts at the restriction point by catalyzing phosphorylation of the Rb protein. Mitotic Cdk-cyclin acts at the G2-M boundary by catalyzing the phosphorylation of proteins involved in chromosome condensation, nuclear envelope breakdown, and spindle assembly. The same mitotic Cdk-cyclin also influences the metaphase-anaphase transition by catalyzing the phosphorylation of the anaphase-promoting complex, which in turn triggers chromosome separation and the breakdown of mitotic cyclin. Checkpoint pathways that monitor the cell for DNA damage, DNA replication, and chromosome attachment to the spindle can send signals that halt the cell cycle at one or more of these key transition points.





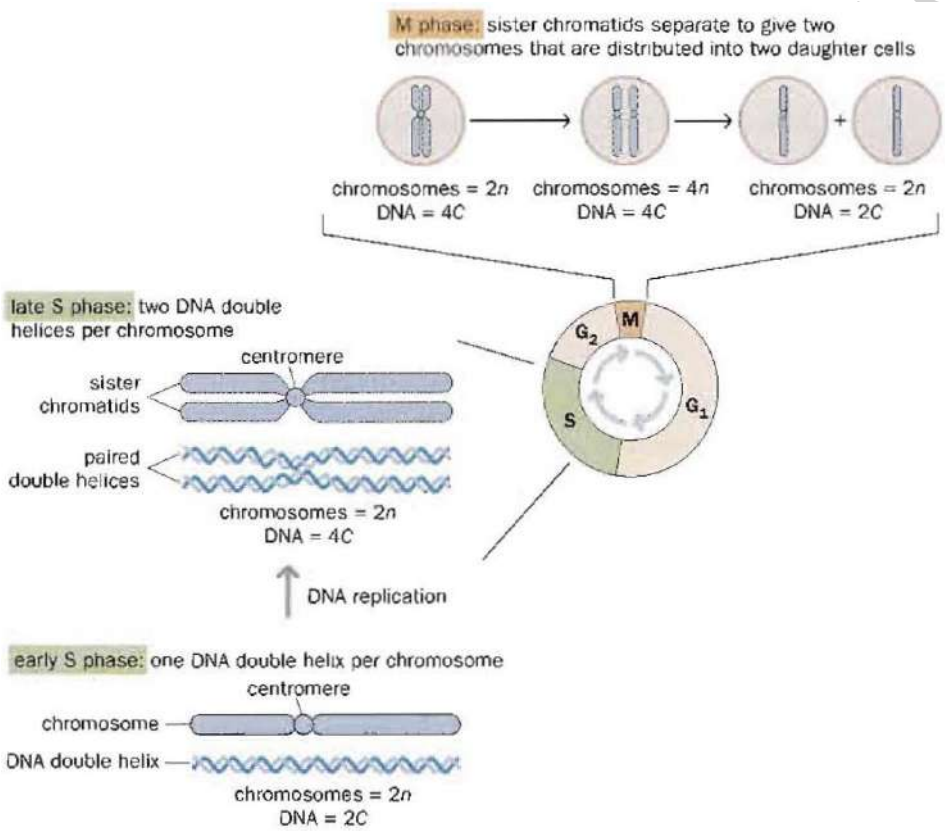


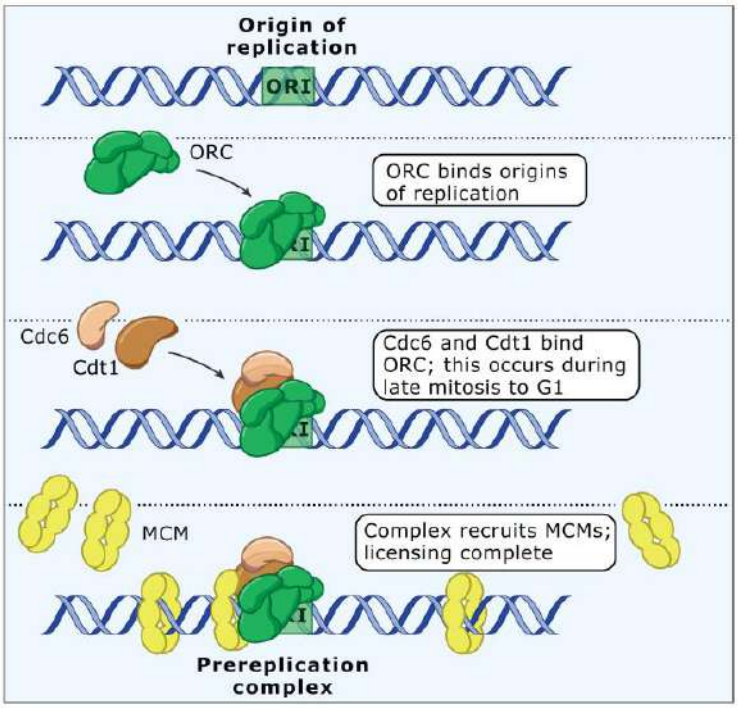
Figure 2.1 Changes in chromosomes and DNA content during the cell cycle. The cell cycle shown at the right includes a very short M phase, when the chromosomes become extremely highly condensed in preparation for nuclear and cell division. Afterwards, cells enter a long period of growth called interphase, during which chromosomes are enormously extended so that genes can be expressed. Interphase is divided into three phases: G_1, S (when the DNA replicates), and G_2. Chromosomes contain one DNA double helix from the end of M phase right through until just before the DNA is duplicated in S phase. After the DNA double helix has been duplicated, the two resulting double helices are held together tightly along their lengths (by specialized protein complexes called cohesins) until M phase. As the chromosomes condense at M phase they are now seen to consist of two sister chromatids, each containing a DNA duplex, that are bound together only at the centromeres. During M phase the two sister chromatids separate to form two independent chromosomes that are then equally distributed into the daughter cells.

A. MODE OF ACTION OF CELL CYCLES CHECK POINTS

1. A sensor detects a defect in an event
2. A signaling molecule that transmits a signal upon detection of an error
3. Target that is a part of a cell cycle engine is controlled to halt cell cycle progression

B. RESTRICTION OF DNA REPLICATION:

1. To initiate DNA replication, a **prereplication complex (pre-RC)** must be assembled on the origin. It begins with the binding of a six-protein complex, **the origin recognition complex (ORC)**, to the DNA. ORC mark a potential origins but is not sufficient for activation.
2. It serves as a platform for binding of two other conserved proteins: Cdc6, which belongs to the family of AAA+ ATPases, andCdt1. (Many proteins with ATPase domains use the energy liberated by ATP hydrolysis to perform work.)
3. The **minichromosome maintenance complex (MCM)**, a ring made up of six closely related proteins that are also members of the large AAA+ ATPase family, is recruited next.
4. The MCMs are abundant, and MCM complexes may spread beyond the origin.
5. Once MCMs are loaded, ORC and Cdc6 are dispensable, and the pre-RC is poised for activation.



6. Assembly of **the pre-RC is restricted to the window between the end of M phase and early S phase by several mechanisms**.
   i. **First**, the amount of Cdc6 protein is controlled so it is available only during this time.
   ii. **Secondly** the ***Cdt1 protein is negatively regulated by a protein called geminin***, which prevents its activity outside of the G1 window.
   iii. **Finally**, pre-RC assembly itself is restricted by mitotic CDK-cyclin activity.
7. The CDK-cyclin complex targets subunits of ORC, Cdc6, and MCMs. In response to CDK phosphorylation, Cdc6 is inactivated, and CDK phosphorylation of MCMs during S phase correlates with removal of MCMs from the DNA.
8. The pre-RC, therefore, can only be established when CDK-cyclin activity is low, between the times of high mitotic CDK-cyclin activity in M phase and S phase.

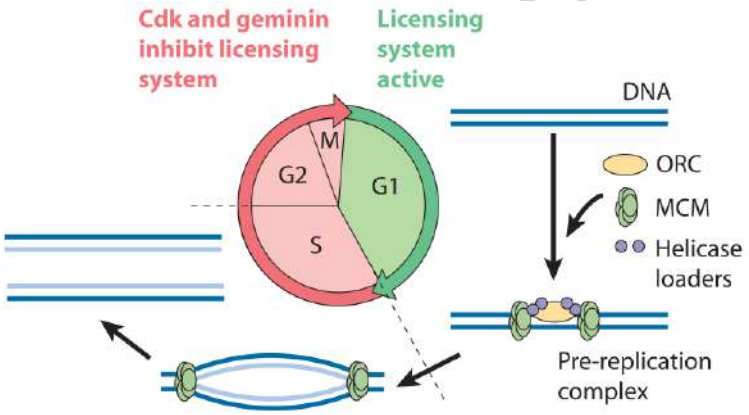
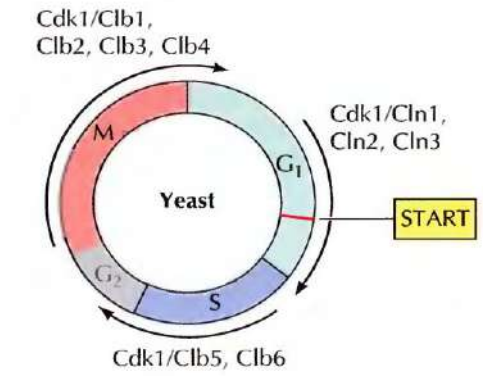
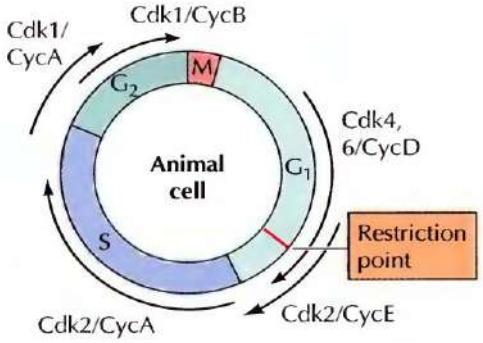


FIGURE 19-32 Key Transition Points in the Cell Cycle. The red bars mark three important transition points in the eukaryotic cell cycle where control mechanisms determine whether the cell will continue to proceed through the cycle. That determination is based on chemical signals reflecting both the cell's internal state and its external environment. The two circular, dark green arrows indicate locations in late G1 and late G2 where the cell can exit from the cycle and enter a nondividing state.





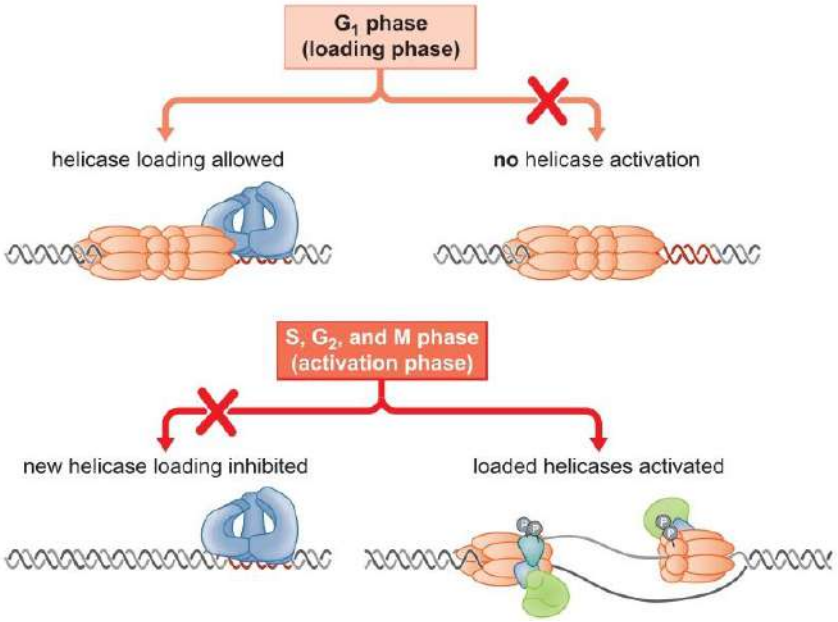
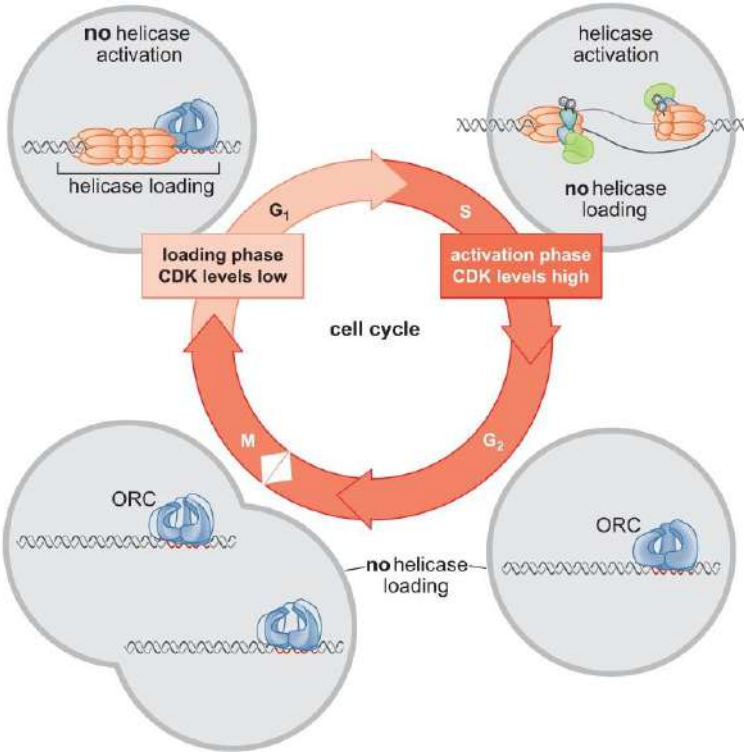


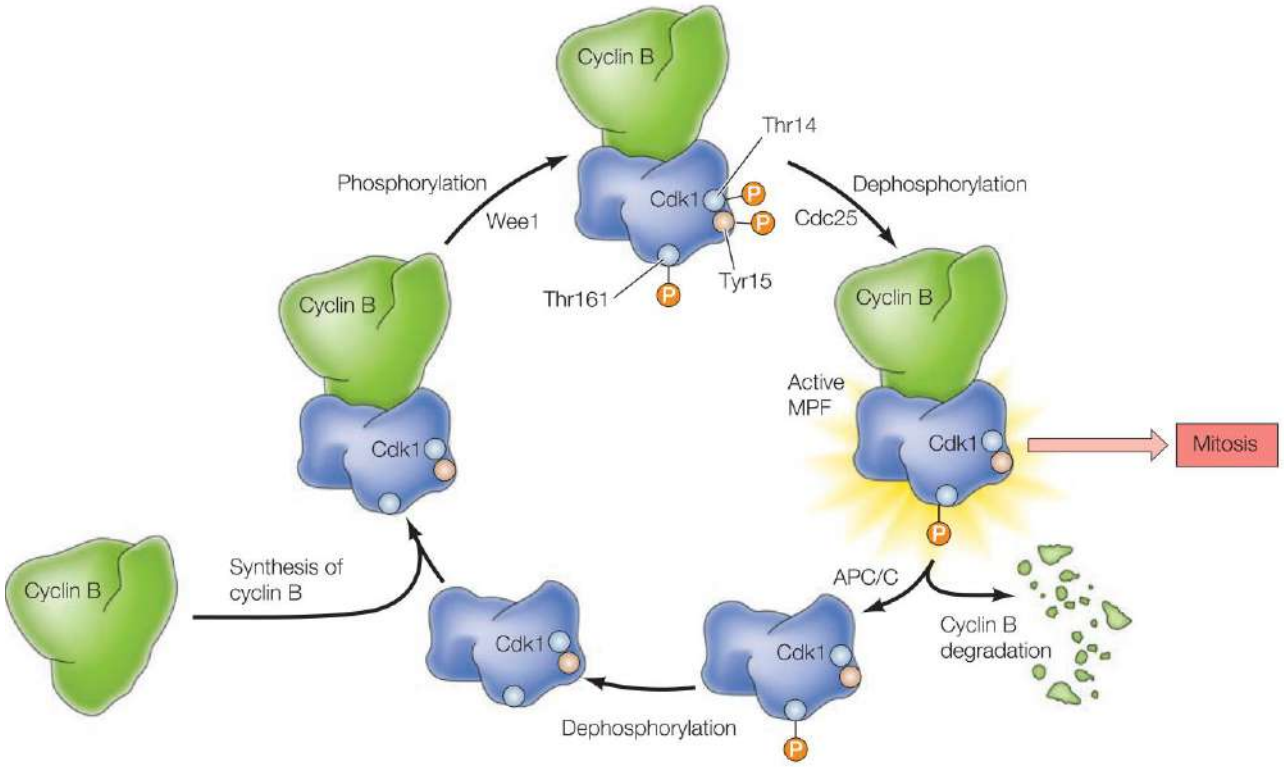
FIGURE 9-33 Eukaryotic helicase loading and activation occur during different cell cycle stages. During the G_1 phase of the cell cycle, helicase loading is permitted, but helicase activation is not allowed. During the remainder of the cell cycle (S, G_2, and M phases), helicase loading is inhibited, but loaded helicases can be activated (this will only occur during S phase because after S phase all loaded Mcm2-7 complexes will be removed from the DNA; see Fig. 9-29).

FIGURE 9-34 Cell cycle regulation of CDK activity controls replication. In *S. cerevisiae* cells, CDK levels tightly regulate helicase loading and activation. During G_1, CDK levels are low, allowing helicases to be loaded, but the loaded helicases cannot be activated (because of the requirement of CDK for this event). During S phase, elevated CDK activity inhibits new helicase loading and activates previously loaded helicases. When a loaded helicase is used for the initiation of replication, it is incorporated into the replication fork and leaves the origin. Similarly, passive replication of origin DNA also removes the helicase from the origin DNA (not shown). Because CDK levels remain high until the end of mitosis, no new helicase loading can occur until chromosome segregation is complete and the daughter cells have returned to G_1. Without a new round of helicase loading, reinitiation is impossible.



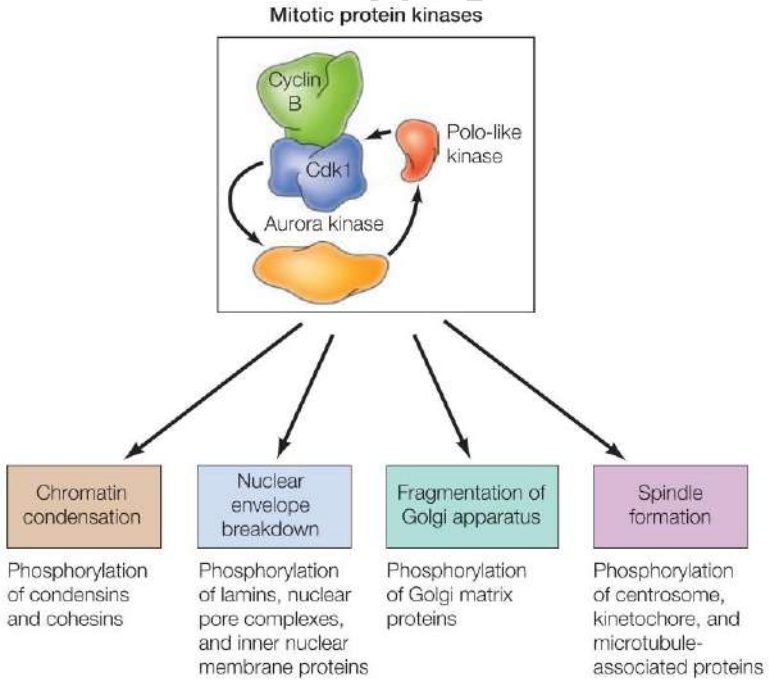
C.MPF

1. In mammalian cells, **cyclin B** is synthesized and forms complexes with ***Cdkl*** during G_2.
2. As these complexes form, Cdkl is phosphorylated at two critical regulatory positions.
   a. One of these phosphorylations occurs on ***threonine-161*** and is ***required for Cdkl kinase activity***.
   b. The second is a ***phosphorylation of tyrosine-15*** and of the adjacent ***threonine-14*** in vertebrates.
3. Phosphorylation of tyrosine-15, catalyzed by a ***protein kinase called Weel,*** inhibits Cdkl activity and leads to the accumulation of inactive Cdkl /cyclin B complexes throughout G2.
4. The transition from **G_2 to M** is then brought about by activation of the Cdkl/cyclin B complex as a result of dephosphorylation of threonine-14 and tyrosine-15 by a protein phosphatase called Cdc25C.
5. Once activated, the Cdkl protein kinase phosphorylates a variety of target proteins that initiate the events of M phase.



D. ENTRY INTO MITOSIS

1. Mitosis involves dramatic changes in multiple cellular components, leading to a major reorganization of the entire structure of the cell. These events are triggered by activation of the Cdk1/cyclin B protein kinase (MPF).
2. Cdk1/cyclin B acts as a master regulator of the M phase transition, both by activating other mitotic protein kinases and by directly phosphorylating some of the structural proteins involved in this cellular reorganization.
3. In particular, mitotic protein kinases of the Aurora kinase (Aurora A and Aurora B) and Polo-like kinase families are activated coordinately with Cdk1 to signal entry into M phase.
4. The Aurora and Polo-like kinases function with Cdk1 in a positive feedback loop, with Cdk1 activating Aurora kinases, which activate Polo-like kinases, which in turn activate Cdk1. All of these protein kinases then play multiple roles in mitosis.



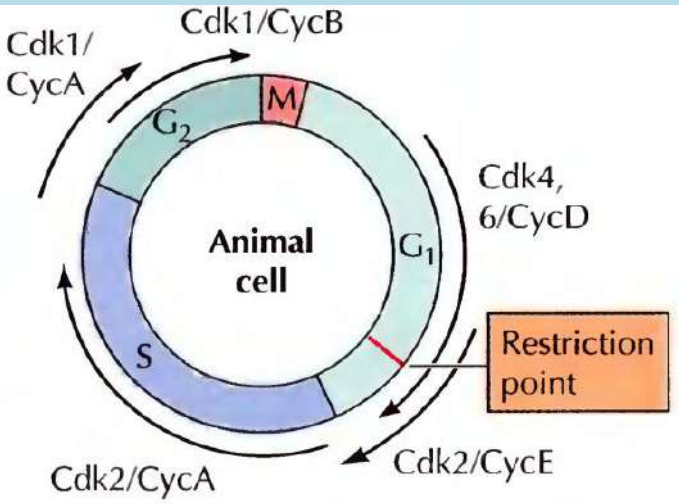
Mitotic protein kinases

The ***mitotic protein kinases Cdk1, Aurora, and Polo-like kinases*** are activated in a positive feedback loop at the onset of M phase.

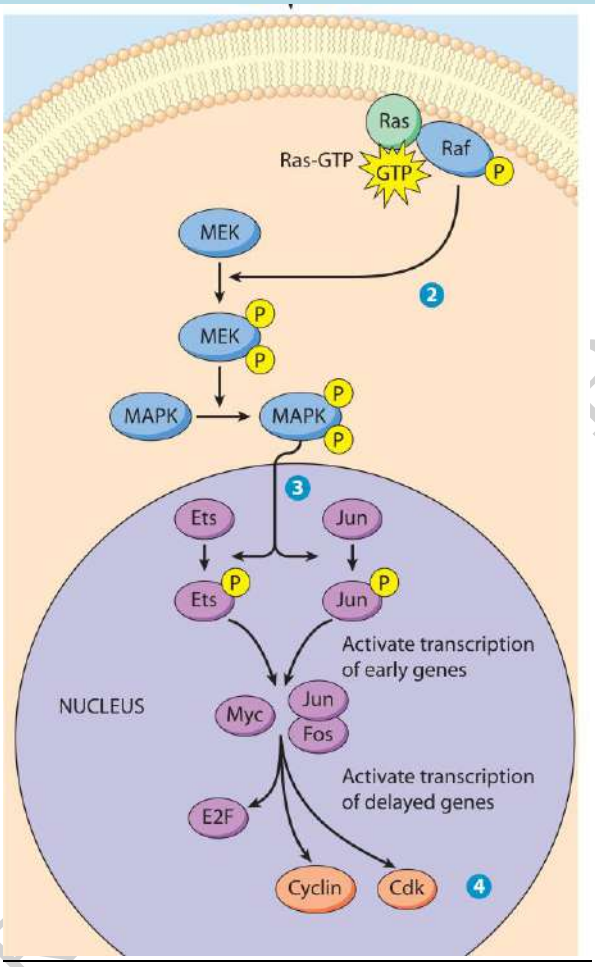
They induce multiple nuclear and cytoplasmic changes during mitosis by phosphorylating proteins such as condensins, cohesins, components of the nuclear envelope, Golgi matrix proteins, and proteins associated with centrosomes, kinetochores, and microtubules.

E. IN ANIMAL CELLS, PROGRESSION THROUGH THE G1 RESTRICTION POINT IS CONTROLLED BY COMPLEXES OF CDK4 AND CDK6 WITH D-TYPE CYCLINS.

1. **Cdk2/cyclin E complexes** function later in G1 and are required for the **G1 to S transition**.
2. **Cdk2/cyclin A** complexes are then required for progression through **S phase**.
3. **Cdkl /cyclin A** regulates progression to **G2**, and
4. **Cdkl/cyclin B** complexes drive the **G2 to M** transition.



F. INDUCTION OF D-TYPE CYCLINS



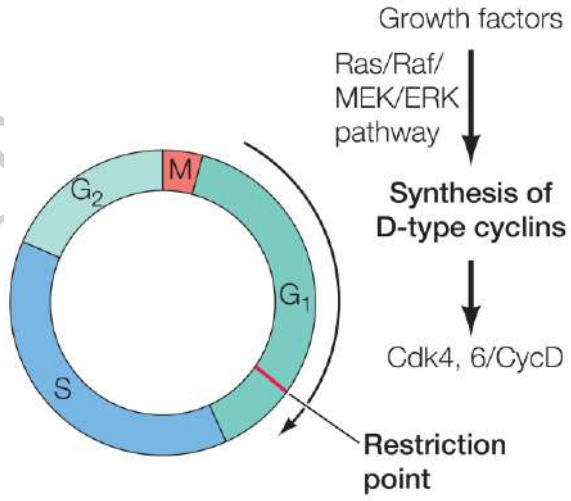


Figure 18.14 Induction of D-type cyclins Growth factors regulate cell cycle progression through the G_1 restriction point by inducing synthesis of D-type cyclins via the Ras/Raf/MEK/ERK signaling pathway (see Figures 17.20 and 17.21).

1. Growth factors regulate cell cycle progression through the G_1 restriction point by inducing synthesis of D-type cyclins via the **Ras/Raf/ MEK/ERK signaling pathway.**
2. One critical link between growth factor signaling and cell cycle progression is provided by the D-type cyclins. Cyclin D synthesis is induced in response to growth factor stimulation, in part by signaling through the ***Ras/Raf/MEK/ERK*** pathway, and cyclin D continues to be synthesized as long as growth factors are present.

However, ***cyclin D is also rapidly degraded during G1 as a result of ubiquitylation by the APC/C ubiquitin ligase***, so its intracellular concentration rapidly falls if growth factors are removed.

3. Thus, as long as ***growth factors are present through G1, complexes of Cdk4,6/cyclin D drive cells through the restriction point***. On the other hand, if growth factors are removed prior to this key regulatory point in the cell cycle ,the levels of cyclin D rapidly fall and cells are unable to progress through G1 to S, instead becoming quiescent and entering G_0.

G. CELL CYCLE REGULATION OF RB AND E2F.

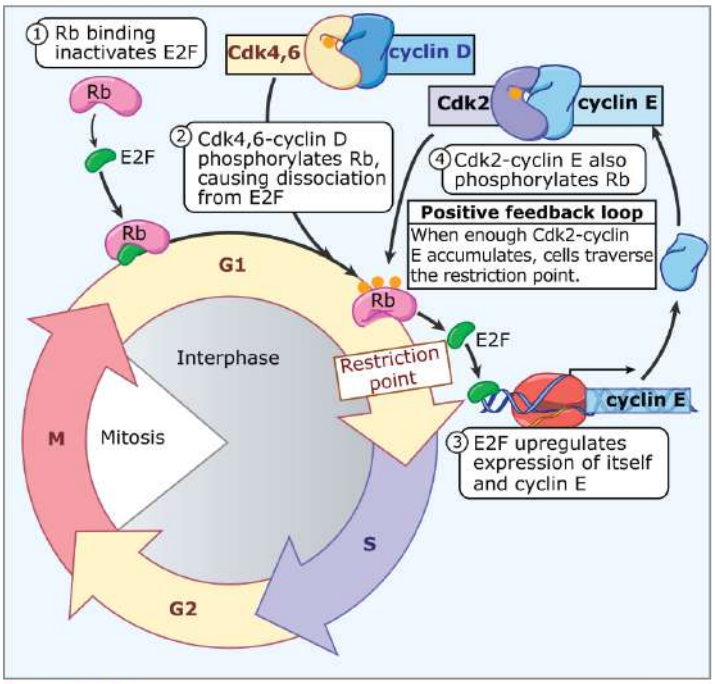
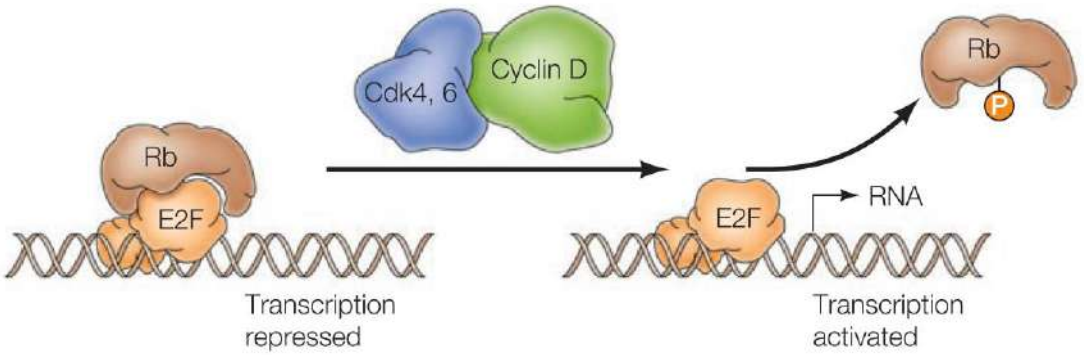


FIGURE 15.19 The transcription factor E2F is inactivated by Rb binding. When Rb is phosphorylated, it cannot bind to E2F, thus allowing E2F to upregulate expression of numerous genes including itself and cyclin E. Cdk2–cyclin E can then phosphorylate more Rb, resulting in an amplification loop.

1. In its under phosphorylated form, Rb binds to members of the E2F family, repressing transcription of E2F-regulated genes.
2. Phosphorylation of Rb by Cdk4, 6/cyclin D complexes results in its dissociation from E2F in late G, E2F then stimulates expression of its target genes, which encode proteins required for cell cycle progression.

1. **Rb is the prototype of a tumor suppressor gene—a gene whose inactivation leads to tumor development**.
2. Whereas oncogene proteins such as ***Ras and cyclin D drive cell proliferation, the proteins*** encoded by many tumor suppressor genes (including Rb and the Ink4 Cdk inhibitors) act as brakes that slow down cell cycle progression.
3. ***Rb binds to members of the E2F family of transcription factors***, which regulate expression of several genes involved in cell cycle progression, including the gene encoding cyclin E.
4. E2F binds to its target sequences in either the presence or absence of Rb. However, Rb acts as a repressor, so the Rb/E2F complex suppresses transcription of E2F-regulated genes. Phosphorylation of Rb by Cdk4, 6/cyclin D complexes results in its dissociation from E2F, which then activates transcription of its target genes.
5. Rb thus acts as a ***molecular switch*** that converts ***E2F from a repressor to an activator of genes required for cell cycle progression***. The ***control of Rb by Cdk4, 6/cyclin D phosphorylation*** in turn couples this critical regulation of gene expression to the availability of growth factors in G_1



H. CDK2/CYCLIN E AND ENTRY INTO S PHASE

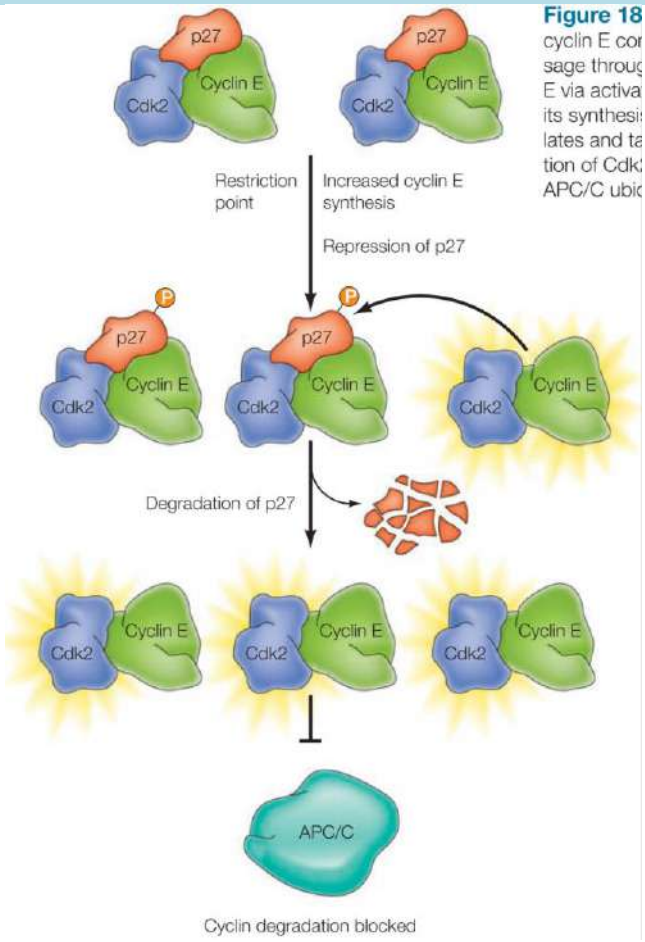


Figure 18 cyclin E cor sage throug E via activa its synthesi lates and ta tion of Cdk APC/C ubic

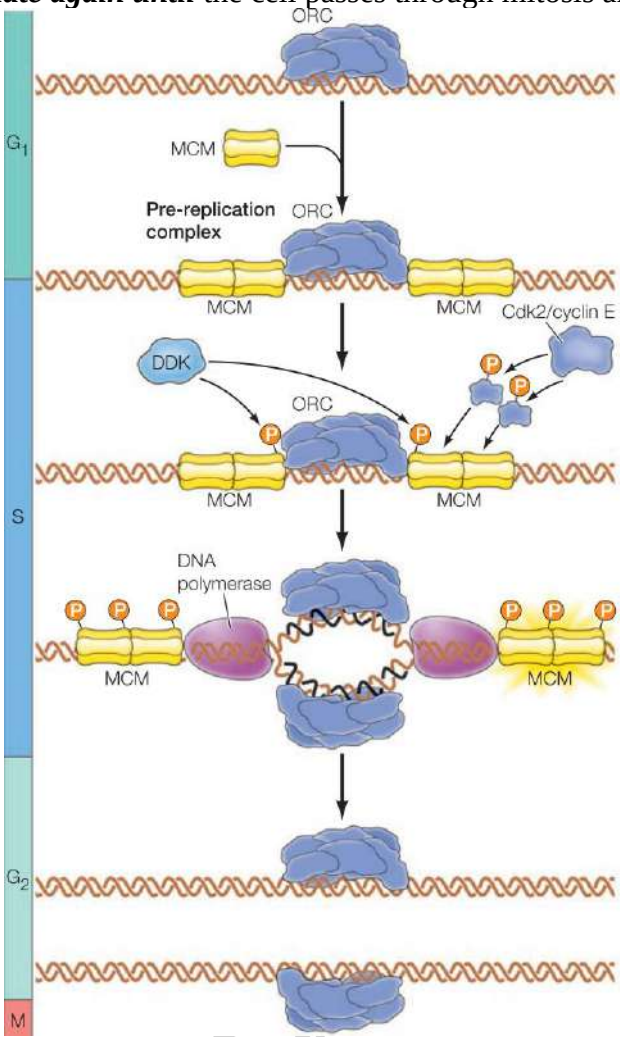
1. In early G1, Cdk2/cyclin E complexes are inhibited by the Cdk inhibitor p27.
2. Passage through the restriction point induces the synthesis of cyclin E via activation of E2F.
3. In addition, growth factor signaling reduces the levels of p27 by inhibiting its transcription and translation.
4. As Cdk2 becomes activated, it phosphorylates and targets p27 for degradation, resulting in further activation of Cdk2/cyclin E complexes. Cdk2/cyclin E also inhibits the APC/C ubiquitin ligase, preventing cyclin E degradation
5. The resulting activation of Cdk2/cyclin E leads to activation of the MCM helicase and initiation of DNA replication.

1. Progression through the restriction point and entry into S phase is mediated by the ***activation of Cdk2/cyclin E complexes***. This results in part from the synthesis of cyclin E, which is stimulated by E2F following phosphorylation of Rb.
2. In addition, the ***activity of Cdk2/cyclin E is inhibited in G_0*** or ***early G_1*** by the ***Cdk inhibitor p27***.
3. This inhibition of Cdk2 by p27 is relieved by multiple mechanisms as cells progress through G1.
4. First, growth factor signaling via both the ***Ras/Raf/MEK/ERK*** and ***PI 3-kinase/Akt pathways*** reduces both the ***transcription and translation of p27***, lowering the levels of p27 within the cell.
5. In addition, once ***Cdk2 becomes activated***, it brings about the ***complete degradation of p27*** by phosphorylating it and targeting it for ubiquitylation. This positive autoregulation further activates Cdk2/cyclin E, which also ***phosphorylates and inactivates the APC/C ubiquitin ligase, preventing cyclin E degradation.***
6. High levels of cyclins and Cdk2 activity are thus maintained, driving progression through S and G2.

I. CDK2/CYCLIN E AND ENTRY INTO S PHASE

1. Cdk2/cyclin E complexes initiate S phase by activating DNA synthesis at replication origins.
2. The initiation of replication at each of these origins must be carefully controlled so that each segment of the genome is replicated once and only once during the S phase of each cell cycle.
3. Thus, once a segment of DNA has been replicated in S phase, control mechanisms exist to prevent reinitiation of DNA replication until the cell cycle has been completed and the cell has passed through mitosis.
4. DNA replication is initiated by the activity of MCM helicase proteins, which is regulated by Cdk/cyclin complexes at different stages of the cell cycle.
5. The MCM helicase proteins bind to replication origins, together with the origin recognition complex (ORC) proteins, during G_1. They remain inactive as a pre-replication complex throughout G_1 and become activated when the cell enters S phase. This *activation of MCM in S phase* results from the ***action of Cdk2/cyclin E, which phosphorylates*** several activating proteins that are recruited to the pre-replication complex.

6. As noted earlier, activation of ***Cdk2/cyclin E*** also leads to ***inhibition of the APC/C ubiquitin ligase***. This ***inhibition*** of APC/C leads to ***activation of a second protein kinase, DDK, which phosphorylates MCM proteins directly.***
7. Activation of the MCM helicase initiates DNA replication and the MCM proteins move away from the origin with the replication fork. The high activity of Cdk's during **S, G_2, and M** phases prevents the MCM proteins from reassociating with replication origins, so ***pre-replication complexes can only re-form during G1, when Cdk activity is low. Thus, once an origin becomes active during S phase, replication at that origin cannot initiate again until*** the cell passes through mitosis and enters the G1 phase of the next cell cycle.

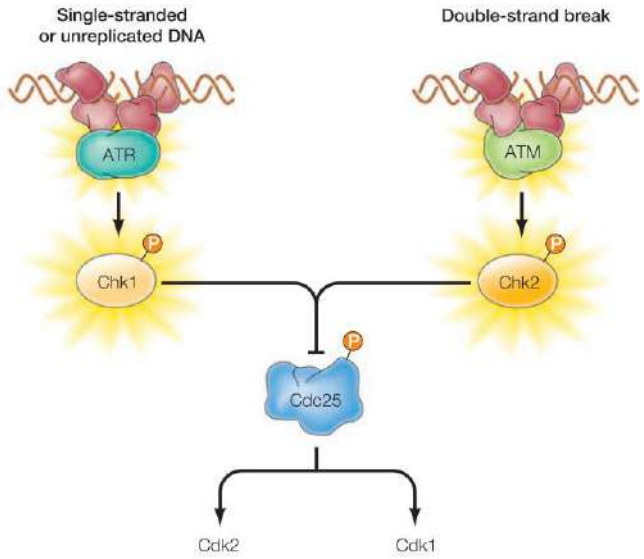


INITIATION OF DNA REPLICATION

1. The MCM helicase proteins bind to origins of replication together with ORC (origin recognition complex) proteins in G_1 to form a pre-replication complex.
2. ***DNA replication is initiated in S phase by Cdk2/cyclin E and the DDK protein*** kinase.
3. ***DDK phosphorylates MCM proteins and Cdk2 phosphorylates additional proteins that join the complex and activate MCM***.
4. Activation of MCM initiates DNA replication and the MCM proteins move away from the origin with the replication fork.
5. The high activity of ***Cdk's prevents the MCM proteins from reassociating with origins during S, G_2, and M, so pre-replication complexes can only re-form during G_1.***

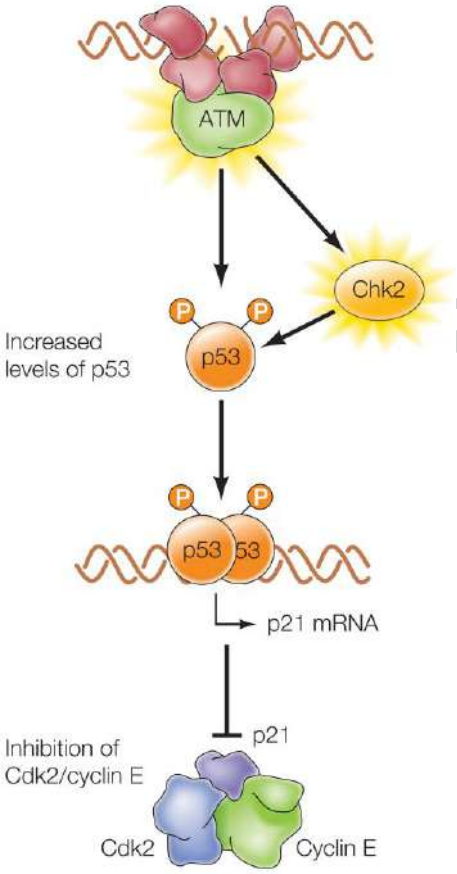
J. CELL CYCLE ARREST AT THE DNA DAMAGE CHECKPOINTS THE ATM AND ATR

1. DNA damage checkpoints play a critical role in maintaining the integrity of the genome by arresting cell cycle progression in response to damaged or incompletely replicated DNA. These checkpoints, which are operative in G_1, S, and G_2 phases of the cell cycle, allow time for the damage to be repaired before DNA replication or cell division proceeds.
2. Cell cycle arrest is mediated by ***two related protein kinases, designated ATR and ATM***, that are activated in response to DNA damage. ATR and ATM then activate a signaling pathway that leads not only to cell cycle arrest but also to the activation of DNA repair and, in some cases, programmed cell death.
3. The importance of this DNA damage response is emphasized by the fact that these proteins were initially identified because mutations in the ***gene encoding ATM*** are responsible for the ***disease ataxia-telangiectasia***, which results in defects in the nervous and immune systems as well as a high frequency of cancer in affected individuals.



1. Cell cycle arrest at the DNA damage checkpoints The ATR and ATM protein kinases are activated in complexes of proteins that recognize damaged DNA.
2. ATR is activated by single-stranded or unreplicatedDNA, and ATM principally by double-strand breaks.
3. ATR and ATM then phosphorylate and activate the Chk1 and Chk2 protein kinases, respectively. Chk1 and Chk2 phosphorylate and inhibit the Cdc25 protein phosphatases.
4. Cdc25 phosphatases are required to activate both Cdk2 and Cdk1, so their inhibition leads to arrest at the DNA damage checkpoints in G_1, S, and G_2.

4. Both ATR and ATM are components of protein complexes that recognize damaged or unreplicated DNA.
5. ATR is activated by single stranded or unreplicated DNA, while ATM is activated by double-strand breaks.
6. Once activated by DNA damage, ATR and ATM phosphorylate and activate the checkpoint kinases Chk1 and Chk2, respectively. Chk1 and Chk2 induce cell cycle arrest by phosphorylating and inhibiting or inducing the degradation of Cdc25 phosphatases.
7. The Cdc25 phosphatases are required. to activate Cdk2 and Cdk1 by removing inhibitory phosphorylations during cell cycle progression. DNA damage thus leads to inhibition of both Cdk2, resulting in cell cycle arrest in G_1 and S, and Cdk1,resulting in arrest in G_2.



Role of p53 in cell cycle arrest

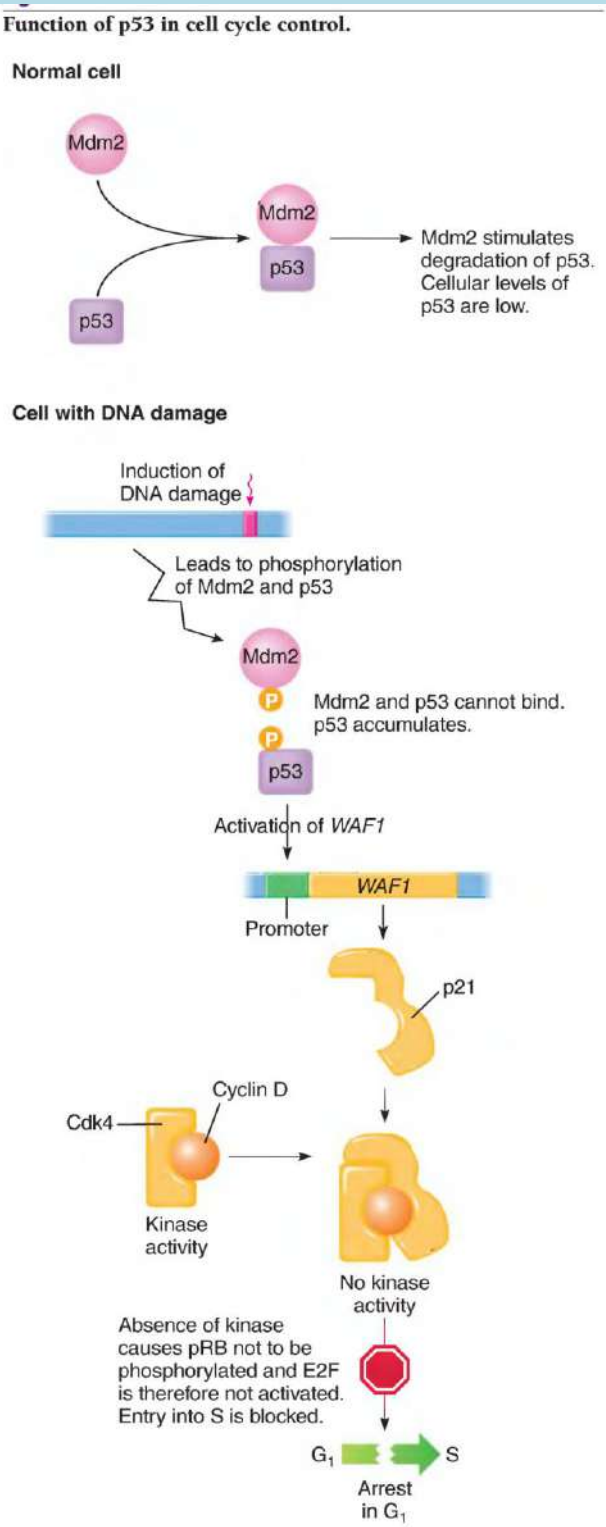
1. The protein p53 plays a key role in cell cycle arrest at DNA damage checkpoints in mammalian cells.
2. Phosphorylation by ATM and Chk2 stabilize p53, resulting in rapid increases in p53 levels in response to DNA damage.
3. The protein p53 then activates transcription of the gene encoding the Cdk inhibitor p21, leading to inhibition of Cdk2/cyclin E or cyclin A complexes and cell cycle arrest.

1. In mammalian cells, arrest at DNA damage checkpoints is also mediated by the action of an additional protein known as p53, which is phosphorylated by both ATM and Chk2.
2. Phosphorylation stabilizes p53, which is otherwise rapidly degraded, resulting in a rapid increase in p53 levels in response to damaged DNA.
3. The p53 protein is a transcription factor, and increased p53 levels lead to the induction of the Cdk inhibitor p21, which inhibits complexes of Cdk2 with cyclin E or cyclin A.

K. TSG p53

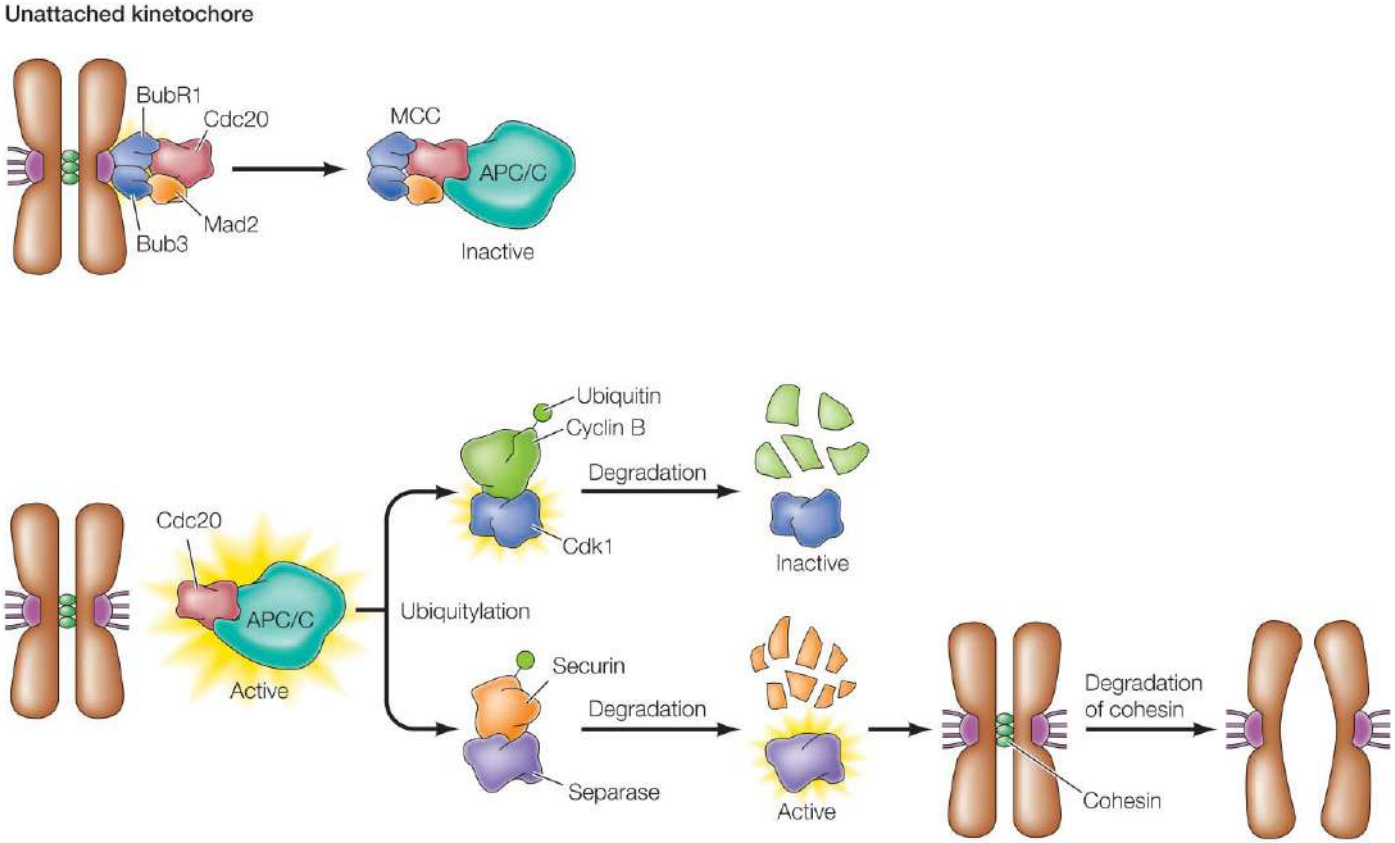
1. **Genetics of the TP53 Tumor Suppressor Gene.**
   a. **The human TP53 gene is at chromosome location 17pl3.1.**
   b. Individuals who inherit one mutant copy of TP53 develop Li-Fraumeni syndrome, a rare form of cancer that is an autosomal dominant trait because the cancer develops when the second copy of TP53 becomes mutated.

2. **Function of p53**.
   a. The **393-amino acid p53 tumor suppressor protein is a transcription factor** that is regulated by phosphorylation and by its interaction with another phosphoprotein, the negative regulator Mdm2 . In a normal cell, both proteins are unphosphorylated, which allows them to bind together.
   b. **Mdm2 stimulates degradation of p53**, and as a result, the amount of p53 in the cell is low. When DNA damage occurs, p53 initiates a cascade of events leading to arrest in G_1. DNA damage results in phosphorylation of both p53 and Mdm2 on the domains where they normally interact. Therefore, a **p53-Mdm2 complex cannot form** and p53 degradation is not promoted, so p53 accumulates.
   c. Functioning as a transcription factor, p53 **turns on transcription of DNA repair genes and of WAF1**, which **encodes a 21-kDa protein called p21**. The p21 protein **binds to the G_1-to-S checkpoint** Cdk4-cyclin D complexes and inhibits their activity. As a result, **pRB in the pRB-E2F complex does not become phosphorylated**, thereby keeping E2F inhibited.
   d. Entry into S is blocked , and the cell arrests in G_1



L. THE SPINDLE ASSEMBLY CHECKPOINT AND PROGRESSION TO ANAPHASE

1. The spindle assembly checkpoint monitors the alignment of chromosomes on the metaphase spindle. Once this
2. has been accomplished, the cell proceeds to initiate anaphase and complete mitosis. The progression from metaphase to anaphase results from ubiquitin mediated proteolysis of key regulatory proteins, triggered by activation of the APC/C ubiquitin ligase.
3. The APC/C is inhibited by Cdk2/cyclin E and A complexes during the S and G_2 phases of the cell cycle. At the beginning of mitosis, ***activation of the APC/C is initiated as a result of phosphorylation by Cdk1/cyclin B***. The APC/C remains inhibited, however, until the cell passes the spindle assembly checkpoint, after which activation of the ubiquitin degradation system brings about the transition from metaphase to anaphase and progression through the rest of mitosis.
4. The spindle assembly checkpoint is remarkable in that the presence of even a single unaligned chromosome is sufficient to prevent activation of the APC/C. The checkpoint is mediated by a complex of proteins (called the ***mitotic checkpoint complex or MCC***) that is formed at unattached kinetochores and inhibits the APC/C.
5. The mitotic checkpoint complex consists of four proteins: ***BubR1, Bub3, Mad2, and Cdc20***. The protein Cdc20 is a required activator of the APC/C, but its activity is blocked when bound by Mad and Bub proteins in the MCC, so formation of the MCC results in
6. inhibition of APC/C. ***Once microtubules have attached to the kinetochores, MCC complexes are no longer formed and Cdc20 is able to activate rather than inhibit the APC/C***.
7. Activation of the APC/C results in ubiquitylation and degradation of two key target proteins that trigger the metaphase to anaphase transition.
8. The onset of anaphase results both from degradation of cyclin B, leading to inactivation of Cdk1, and from degradation of a component of the cohesins, which maintain the connection between sister chromatids while they are aligned on the metaphase plate.



The spindle assembly checkpoint Progression to anaphase is mediated by activation of the APC/C ubiquitin ligase. Unattached kinetochores lead to the assembly of a protein complex (the mitotic checkpoint complex, MCC) that inhibits APC/C. Once all chromosomes are aligned on the spindle, the inhibitory complex is no longer formed and APC/C is activated by Cdc20. APC/C ubiquitylates cyclin B, leading to its degradation and inactivation of Cdk1. In addition, APC/C ubiquitylates securin (an inhibitory subunit of a protease called separase), leading to activation of separase. Separase degrades cohesin, breaking the link between sister chromatids and initiating anaphase.

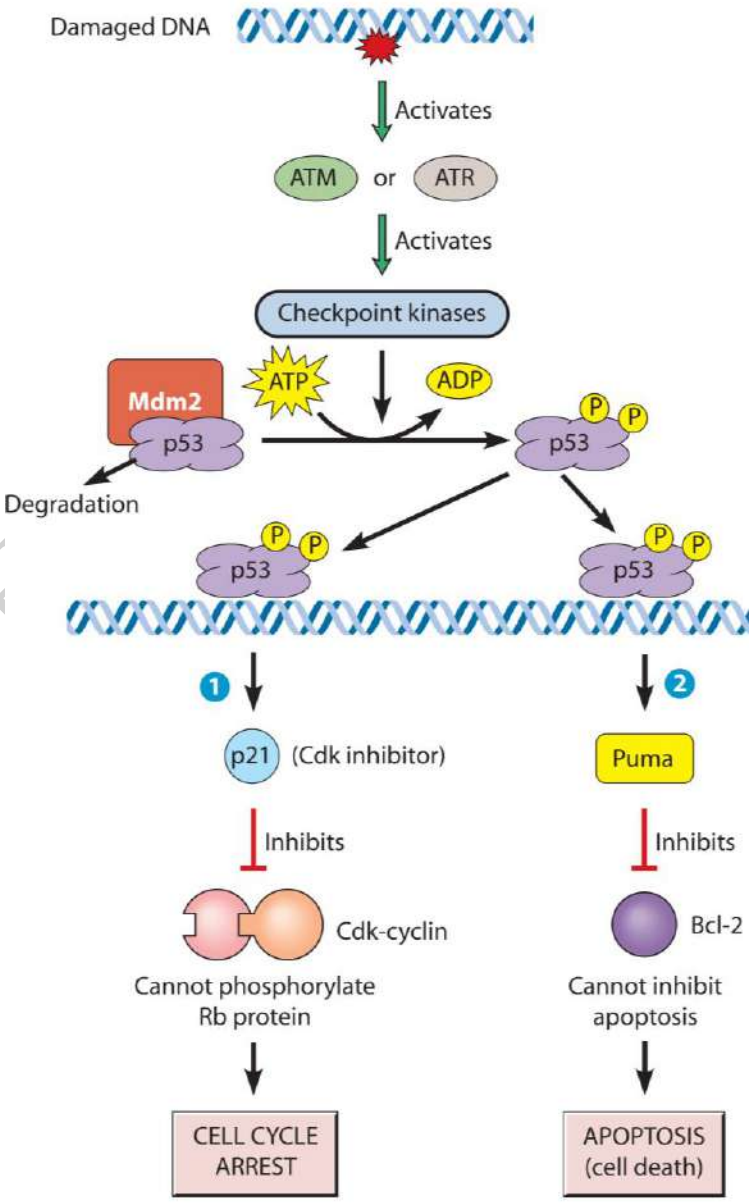
9. Cohesin degradation is not catalyzed directly by the ***APC/C***, which instead ***degrades a protein called securin*** that is an inhibitory subunit of a protease called separase. ***Degradation of securin results in the activation of separase***, which in turn degrades ***cohesin***.

10. Cleavage of cohesin breaks the linkage between sister chromatids, allowing them to segregate by moving to opposite poles of the spindle.
11. The separation of chromosomes during anaphase then proceeds as a result of the action of several types of motor proteins associated with the spindle microtubules. Once the cell has progressed to anaphase, ***the APC/C also triggers the degradation of Aurora and Polo-like kinases***, ***allowing the cell to exit mitosis and return to interphase***. Many of the cellular changes involved in these transitions are simply the reversal of the events induced by Cdk1, Aurora, and Polo-like kinases during mitosis.
12. For example, reassembly of the nuclear envelope, chromatin decondensation, and the return of microtubules to an interphase state result directly from loss of activity of mitotic kinases and dephosphorylation of proteins that had been phosphorylated at the beginning of mitosis.

M. p53-GAURDIAN OF GENOME

Role of the p53 Protein in Responding to DNA Damage.

1. Damaged DNA activates the ***ATM or ATR protein kinase***, leading to activation of checkpoint kinases, which leads to phosphorylation of the p53 protein.
2. ***Phosphorylation stabilizes p53*** by ***blocking*** its interaction with ***Mdm2***, a protein that would otherwise mark p53 for degradation. (it involves Mdm2-catalyzed attachment of p53 to ubiquitin, which targets molecules to the cell's main protein destruction machine, the proteasome.)
3. When the interaction between p53 and Mdm2 is blocked by p53 phosphorylation, the phosphorylated p53 protein accumulates and ***triggers two events.***
   i. The p53 protein binds to DNA and activates transcription of the gene coding for the p21 protein, a Cdk inhibitor. The resulting inhibition of Cdk-cyclin prevents phosphorylation of the Rb protein, leading to cell cycle arrest at the restriction point.
   ii. When the DNA damage cannot be repaired, p53 then activates genes coding for a group of proteins that trigger cell death by apoptosis. A key protein is Puma, which promotes apoptosis by binding to, and blocking the action of, the apoptosis inhibitor, Bcl-2.



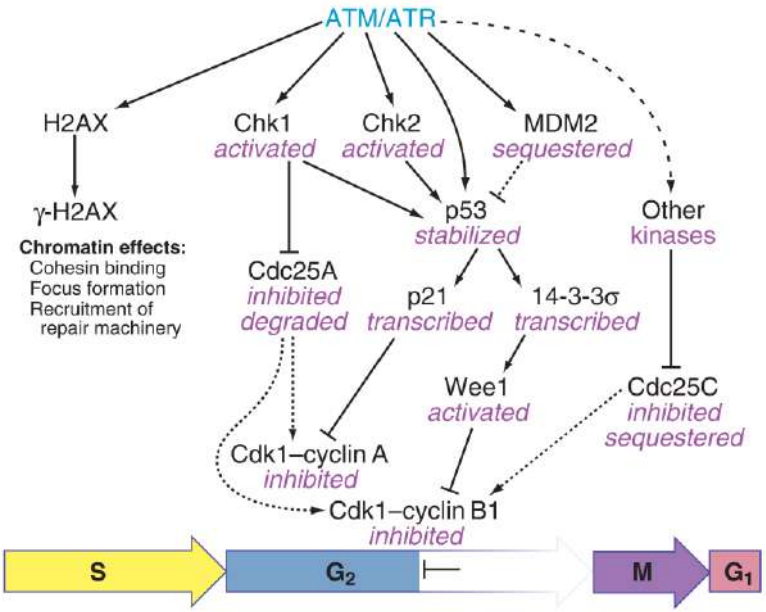


FIGURE 43.11 THE G_2/M CHECKPOINT BLOCKS THE G_2/M TRANSITION FOLLOWING ACTIVATION OF ATM AND/OR ATR BY DNA DAMAGE. *Dotted lines* show activities that are switched off by the checkpoint. The *dashed line* between ATM/ATR and the kinase that inhibits Cdc25C indicates that this pathway is not yet known. (Based on an original figure by Helen Piwnica-Worms.)