

Cell Growth Control

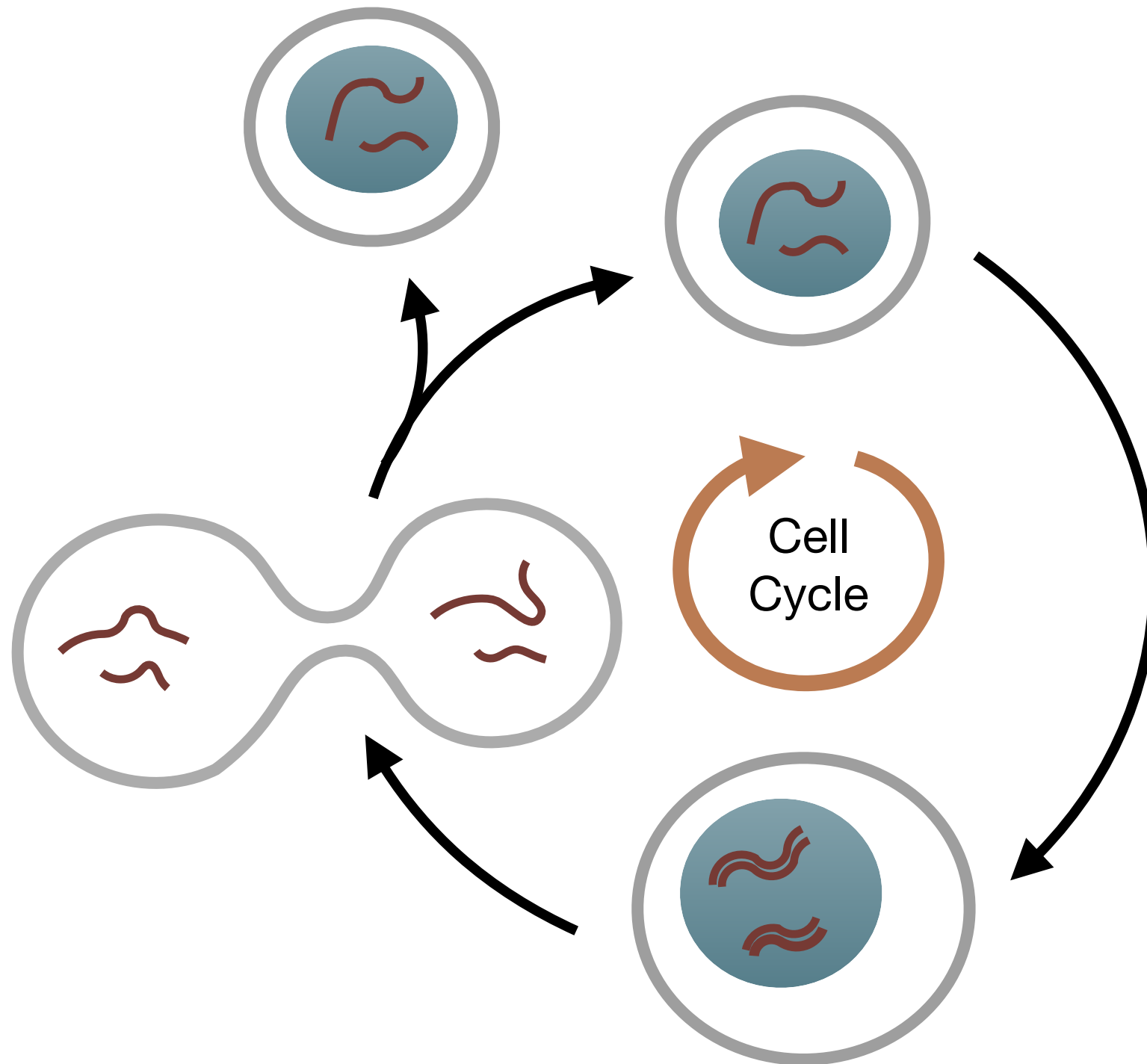
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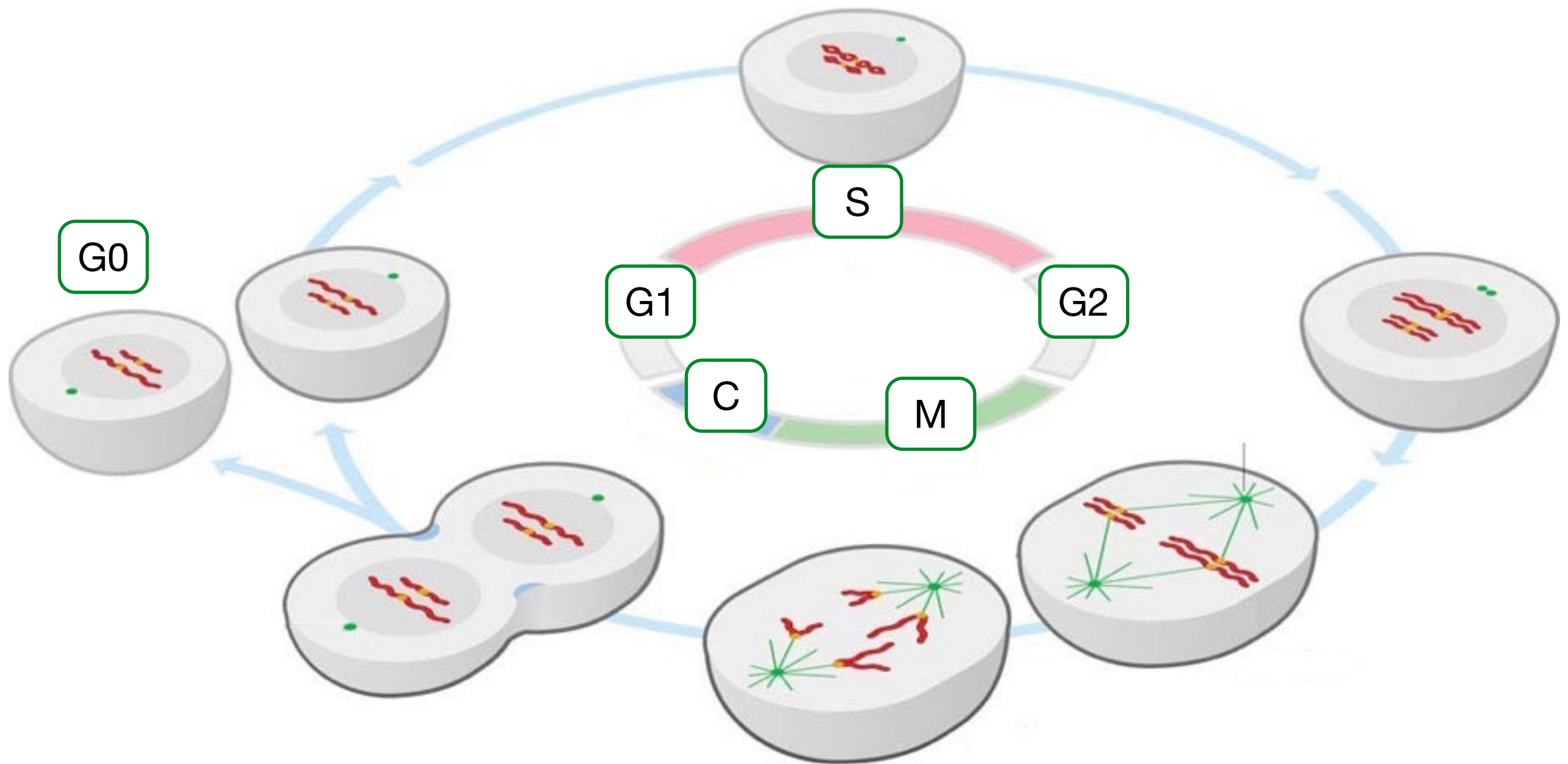
What we'll talk about...

- Cyclin and cyclin-dependent kinases and control of the cell cycle
- Start and regulation of cell division
- Signaling pathways that stimulate and inhibit cell division
- Checkpoints and regulation of the cell cycle
- Mitosis

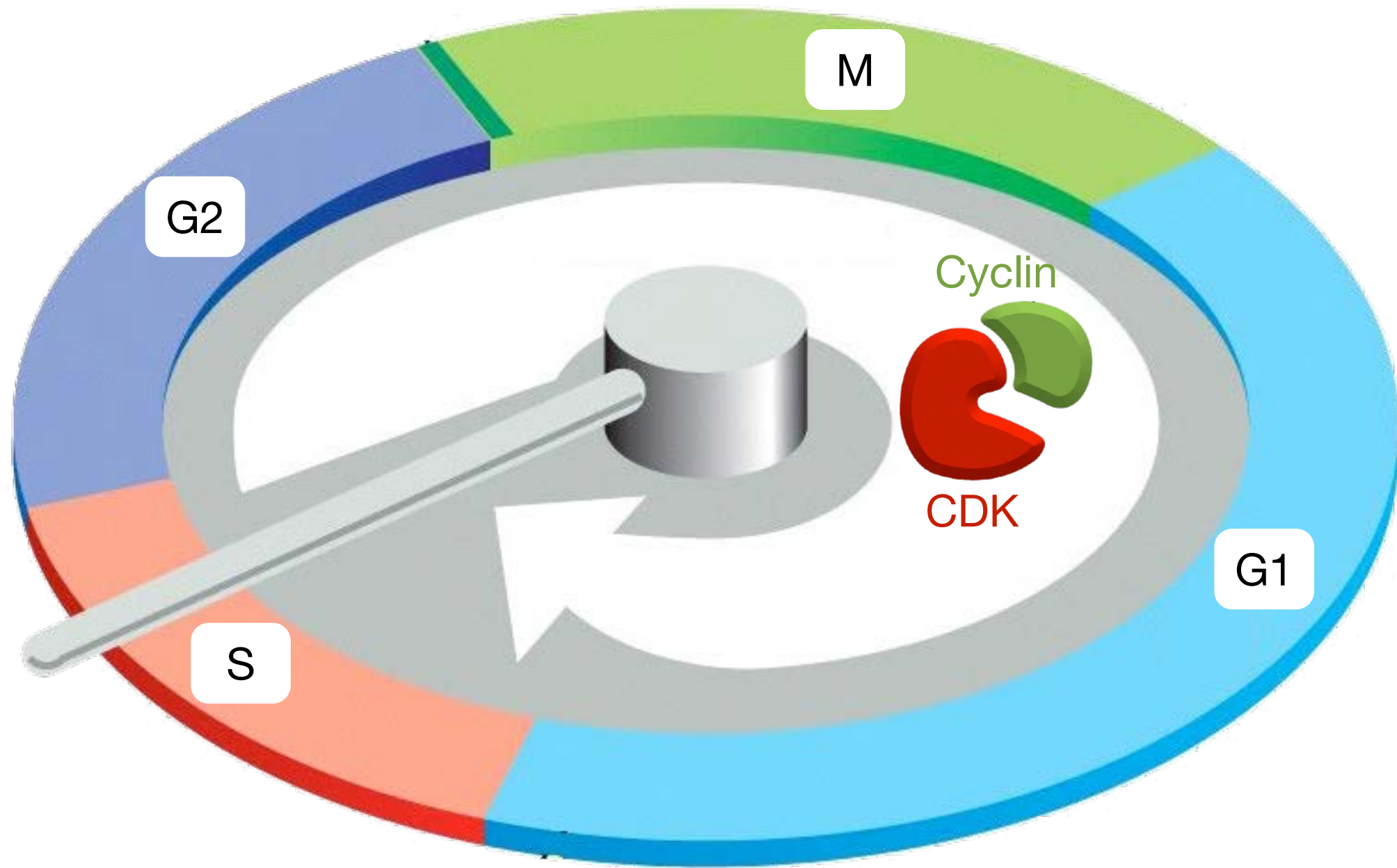
Cell division requires cell growth, chromosome duplication and separation.



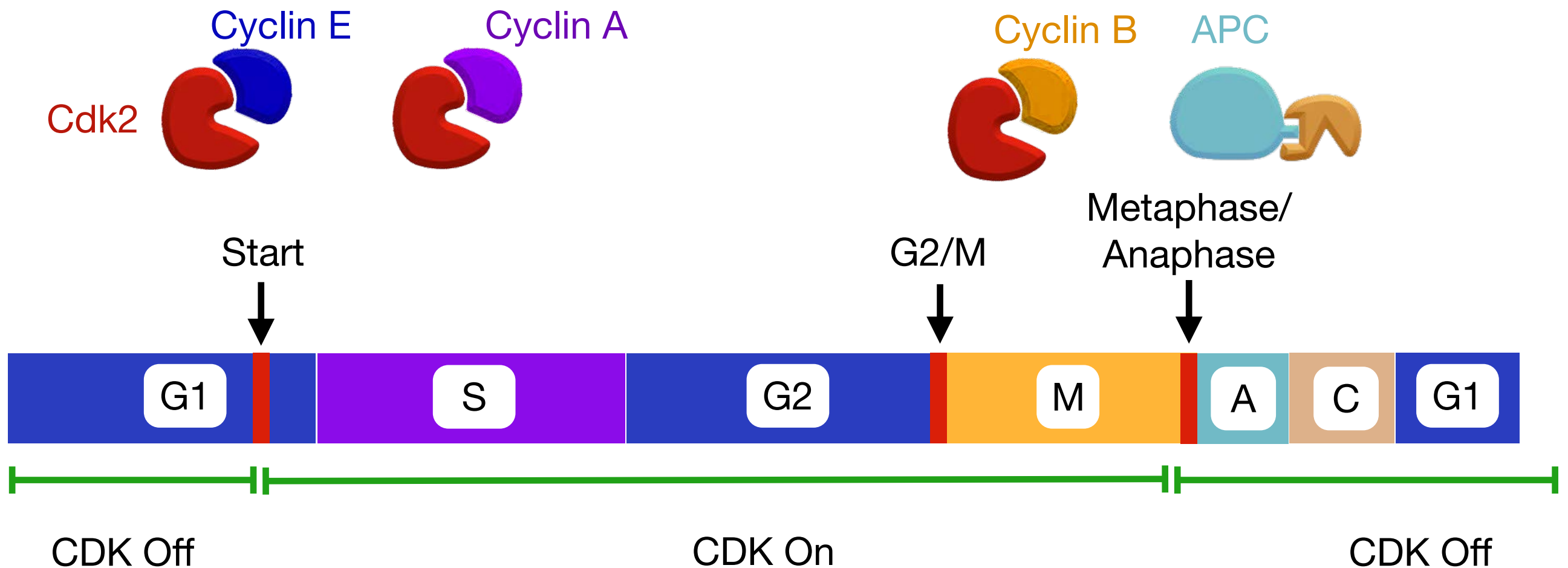
Cell cycle is divided into separate phases.



Cyclins and cyclin dependent kinases (CDK) drive cell cycle events.

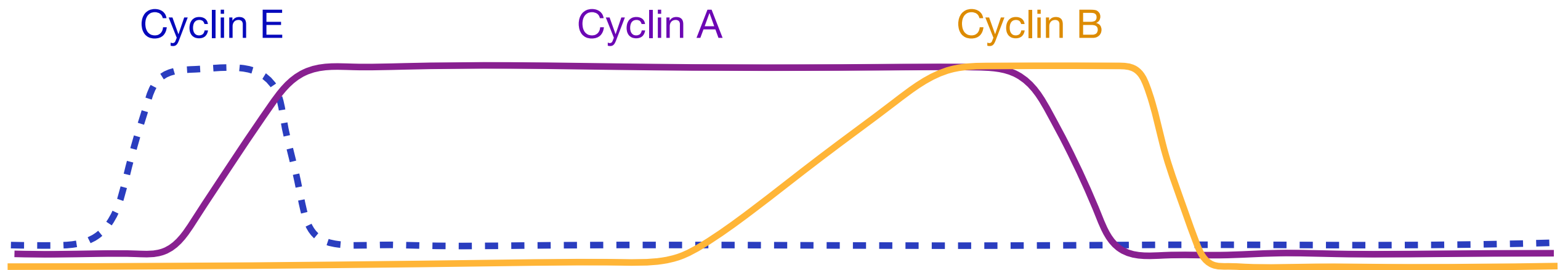


Different cyclin CDK complexes initiate and control the phases of the cell cycle.

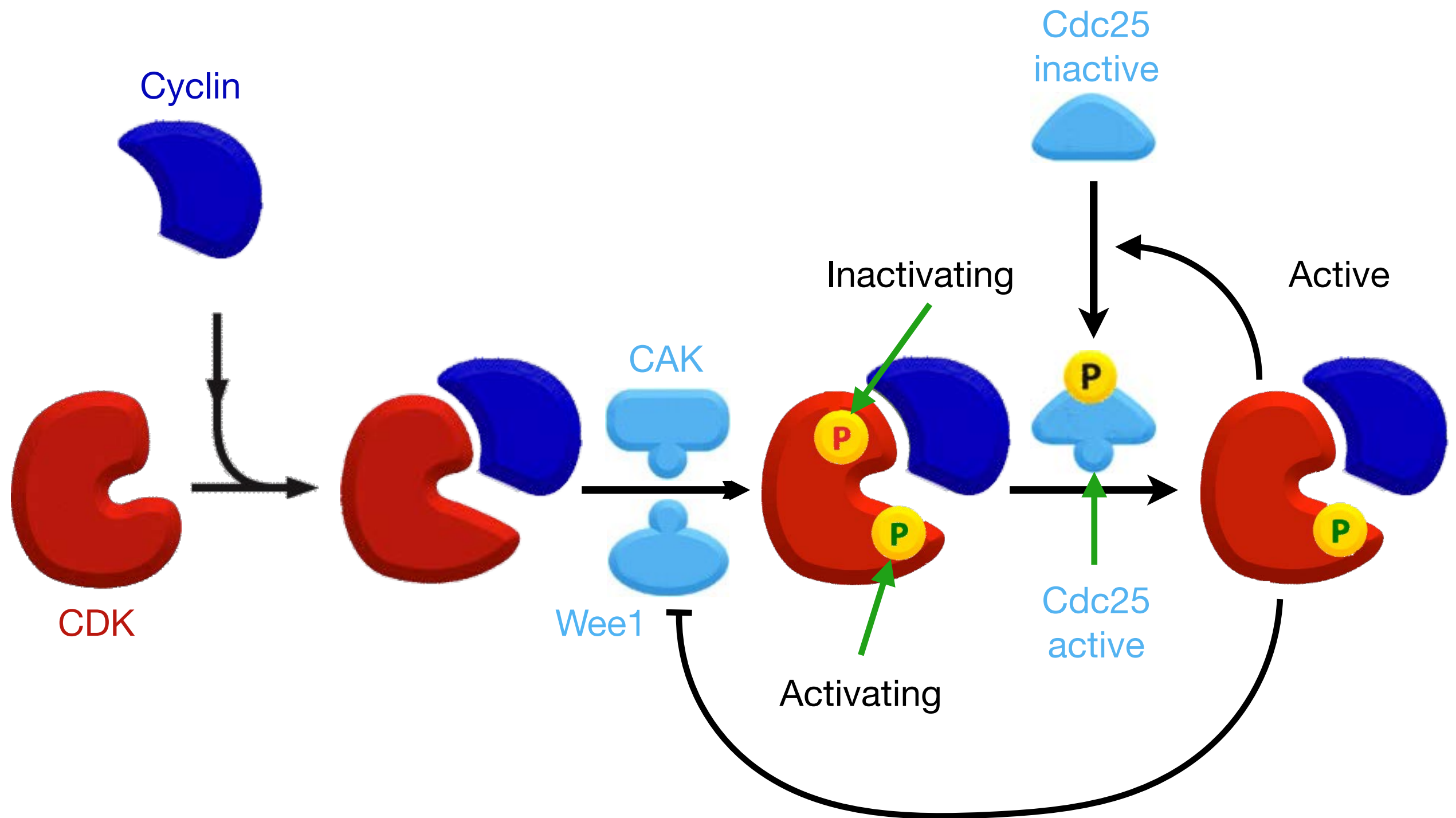


Waves of cyclin expression and degradation mediate ordered progression of cell cycle.

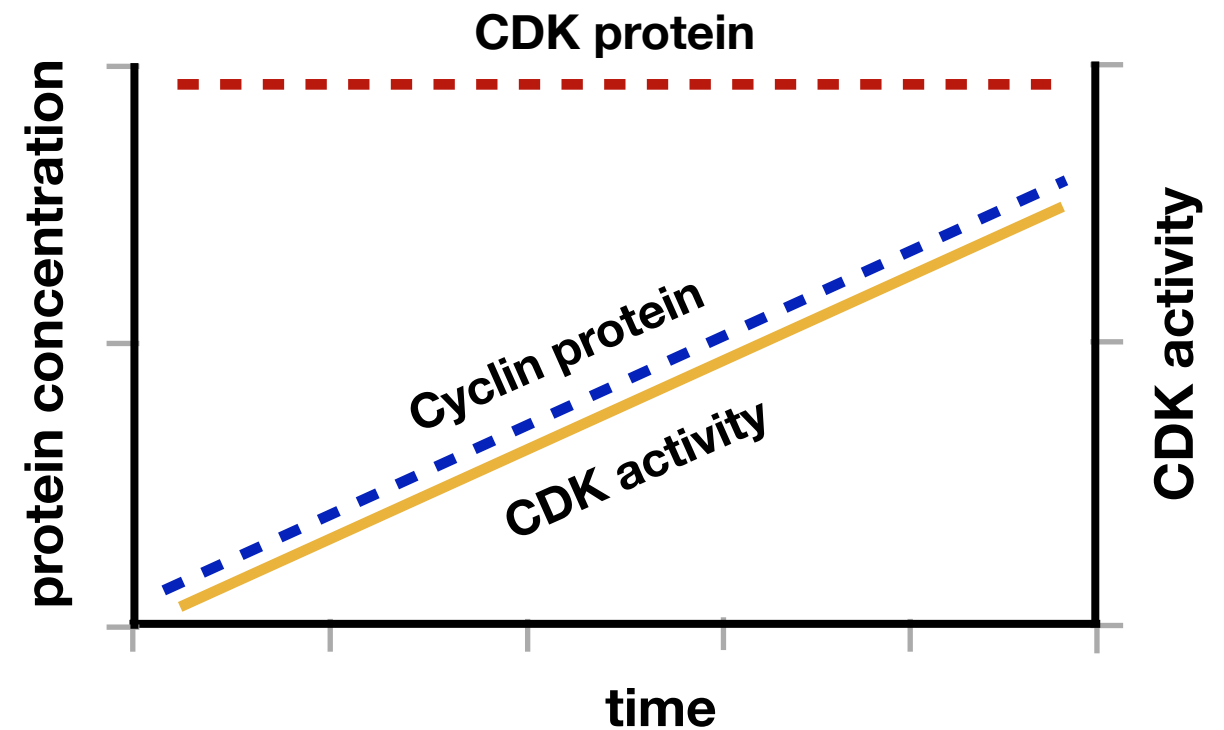
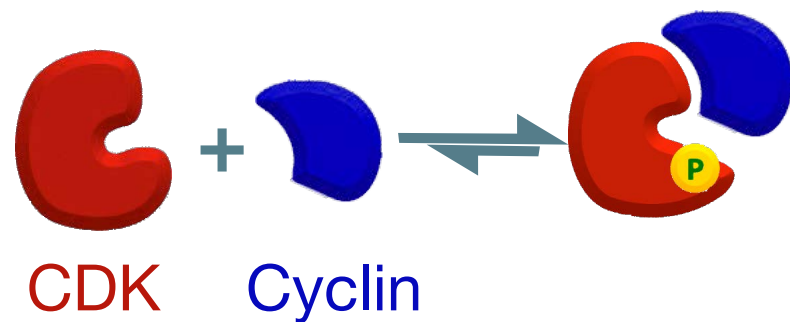
Cyclin protein level



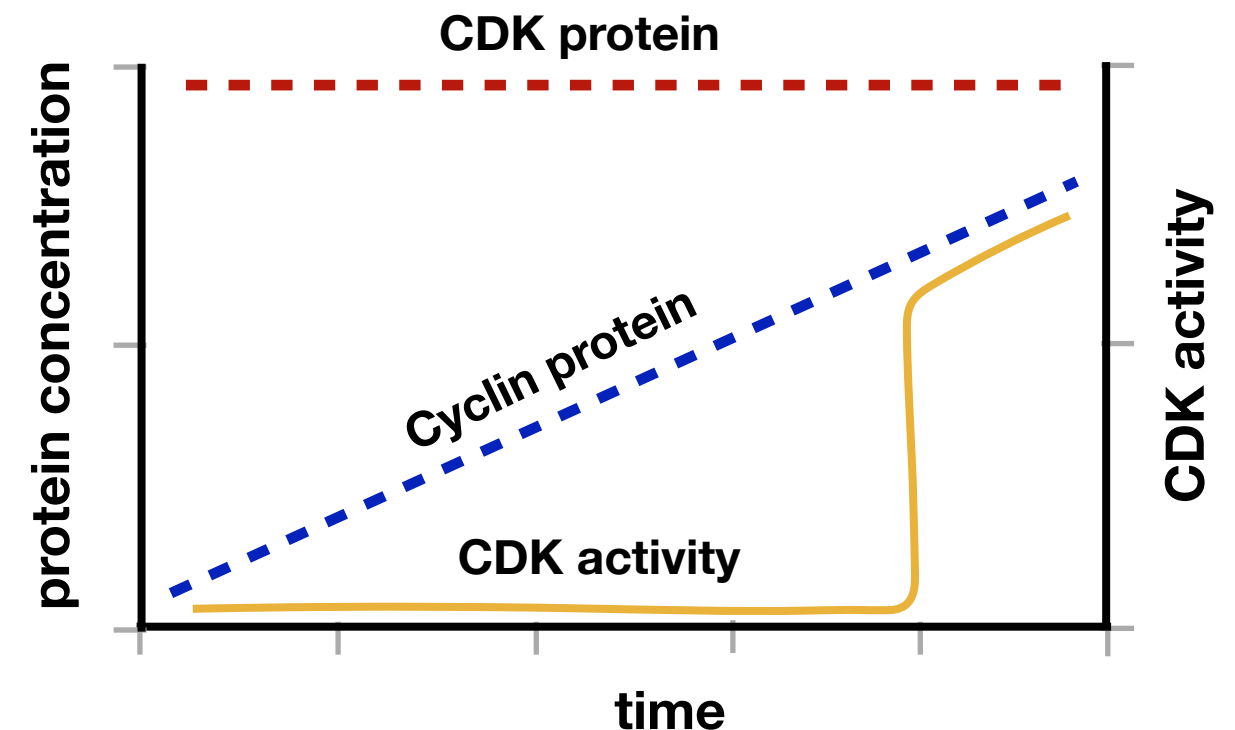
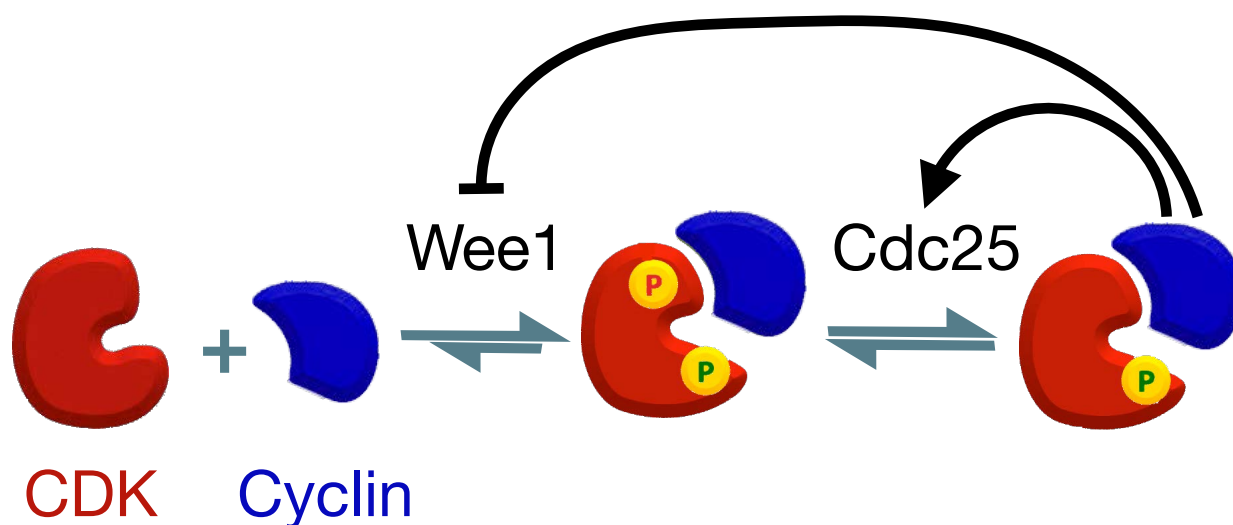
Positive feedback loops increase the amount of active cyclin-CDK.



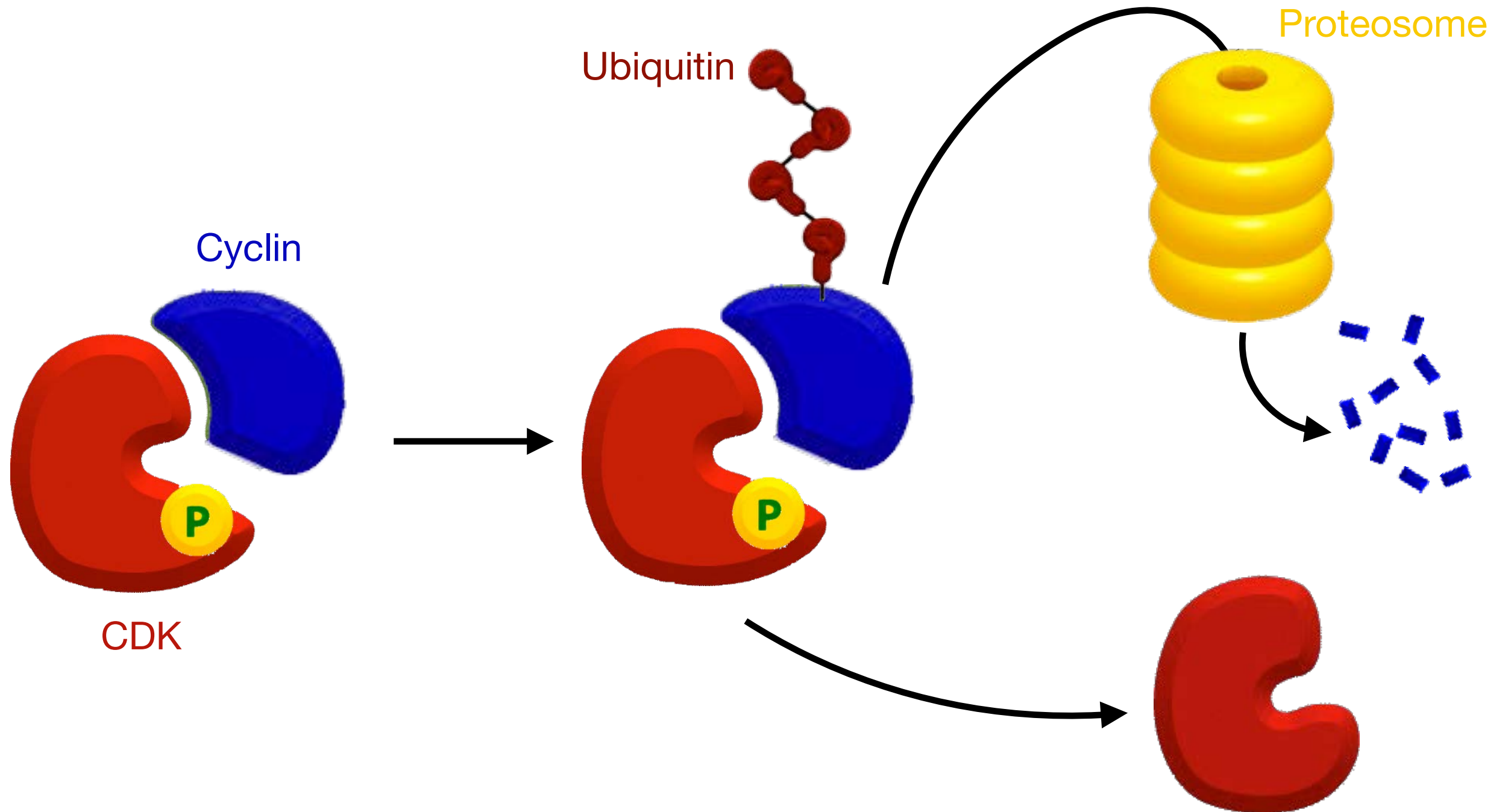
Switch-like activation of CDKs ensures rapid and irreversible initiation of cell cycle events.



Positive Feedback



Ubiquitylation and proteasome are required to digest cyclins and decrease CDK activity.

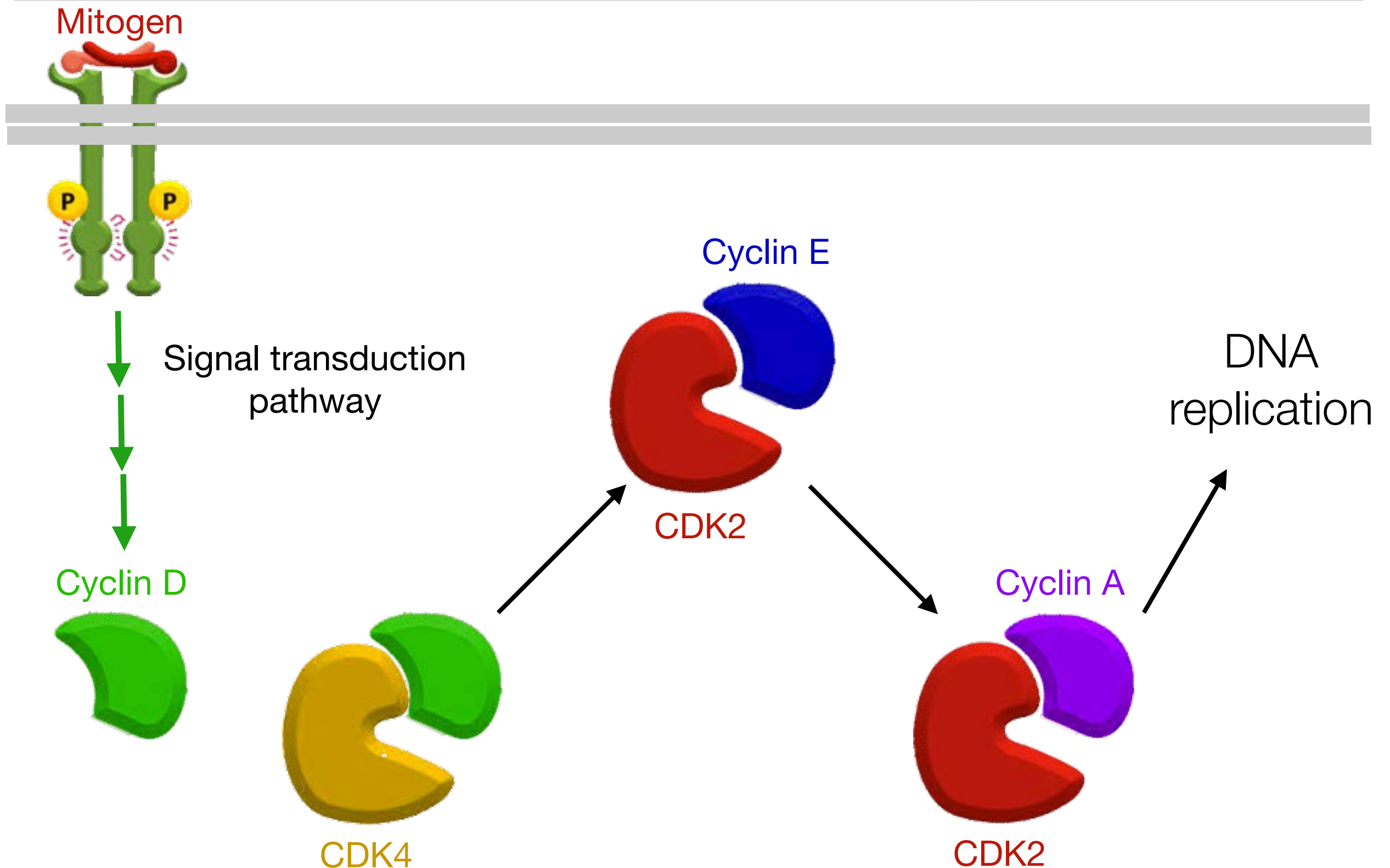


Start and the Decision to Divide

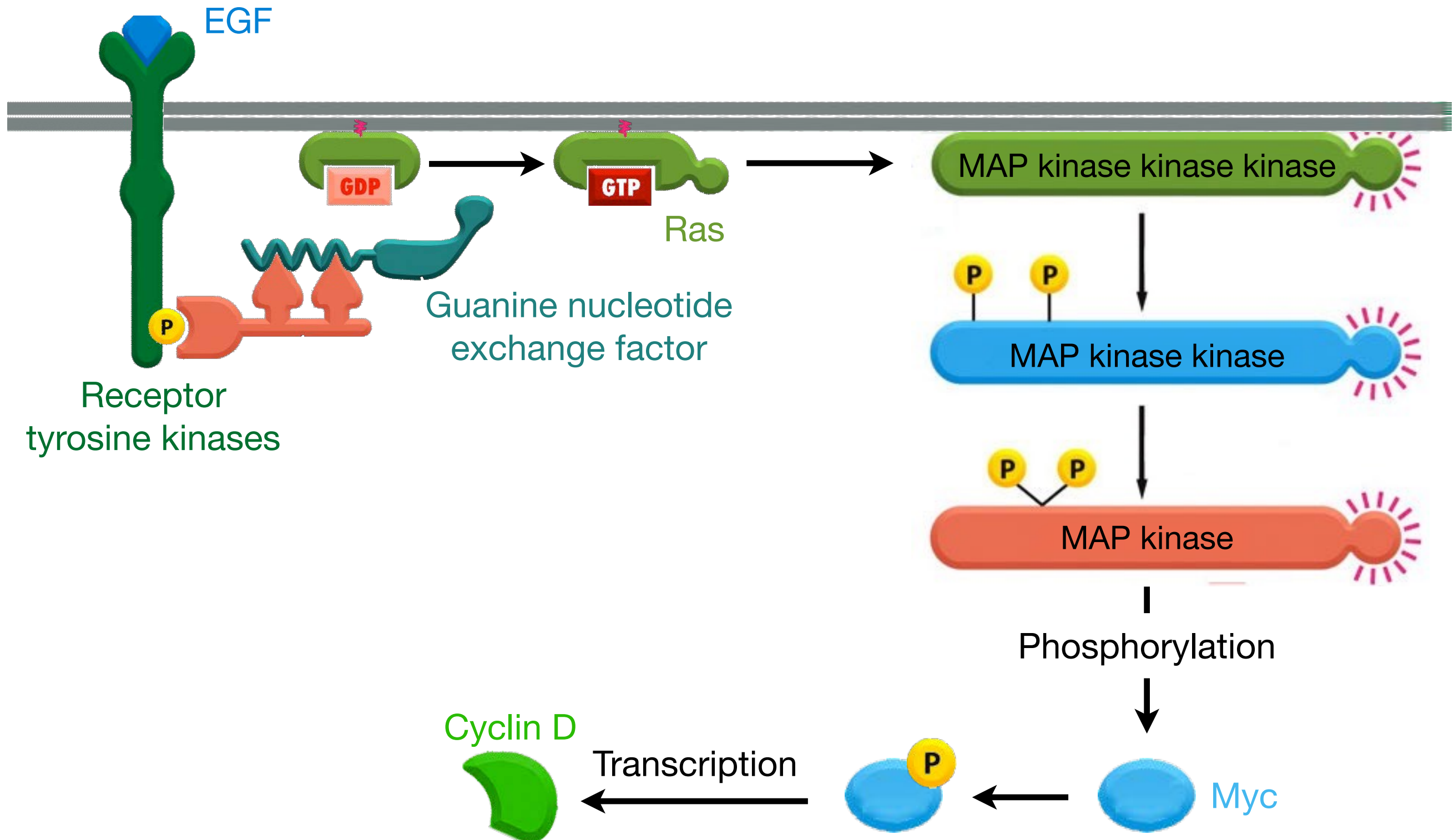
Start marks the initiation of DNA replication and an irreversible commitment to cell division.



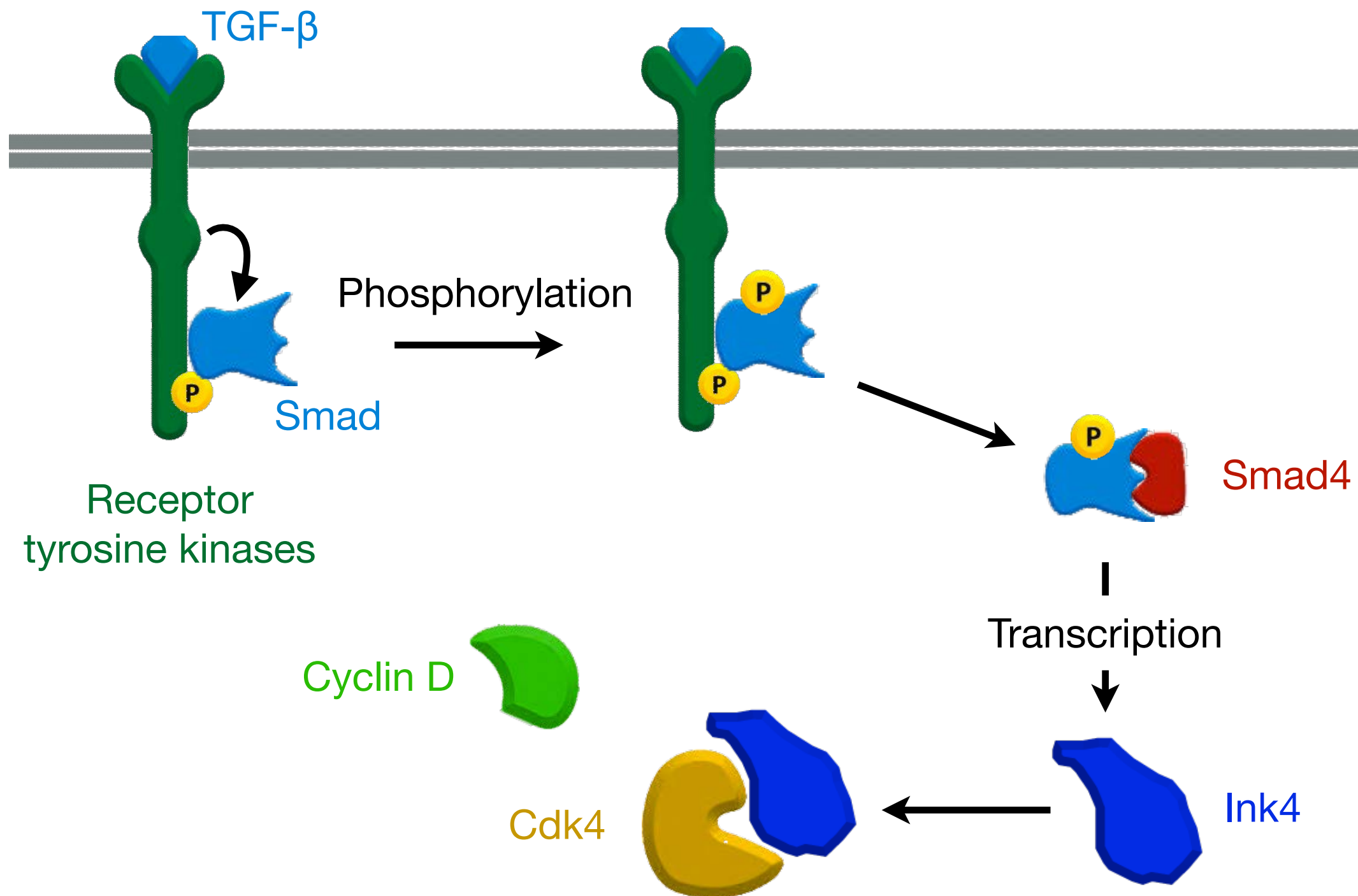
Mitogens activate signaling pathways that lead to expression of Cyclin D.



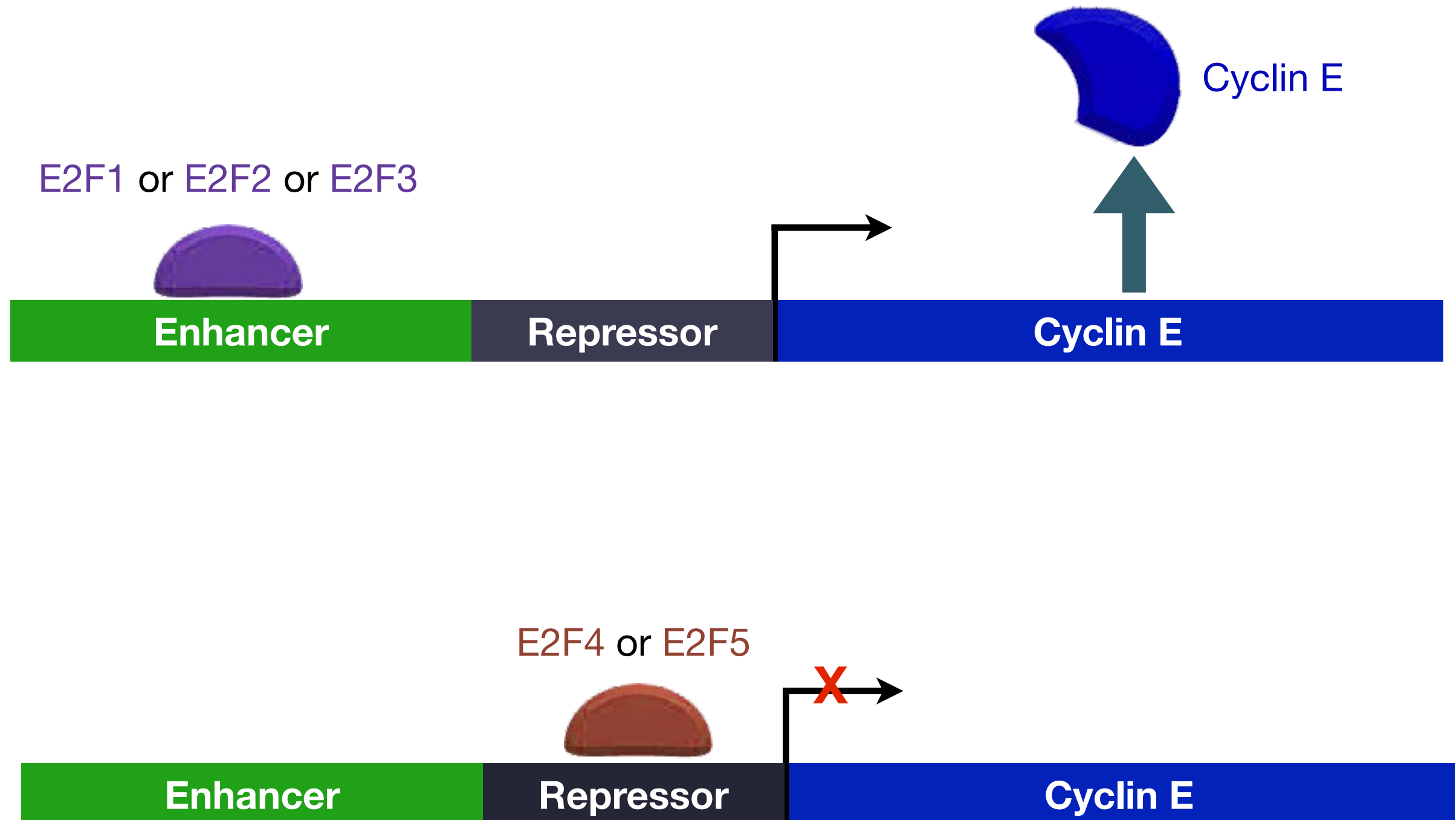
Receptor tyrosine kinases activate MAP kinase pathways to increase expression of cyclin D.



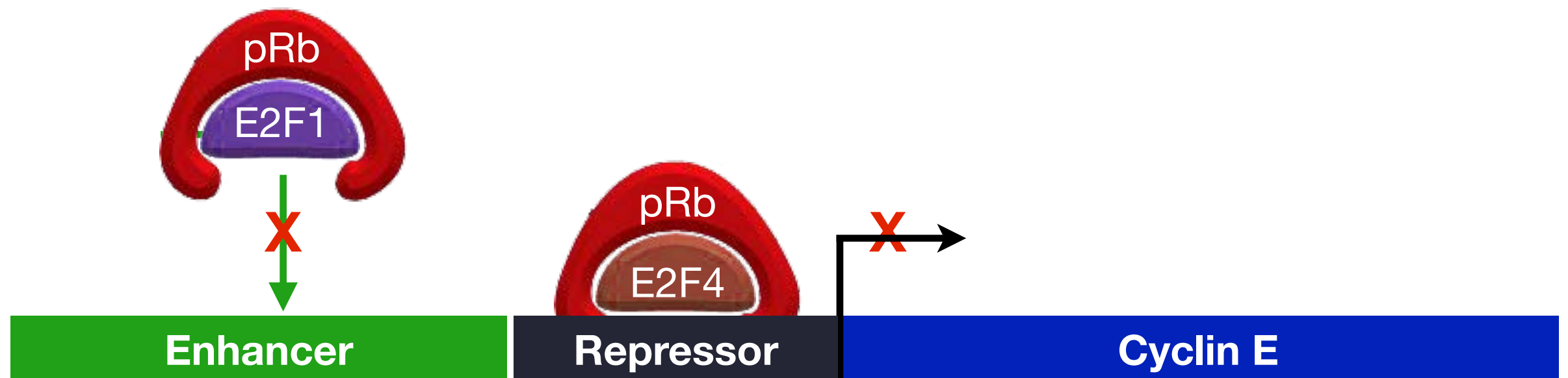
Anti-mitogens activate signaling pathways that inhibit formation of cyclin D-Cdk complexes.



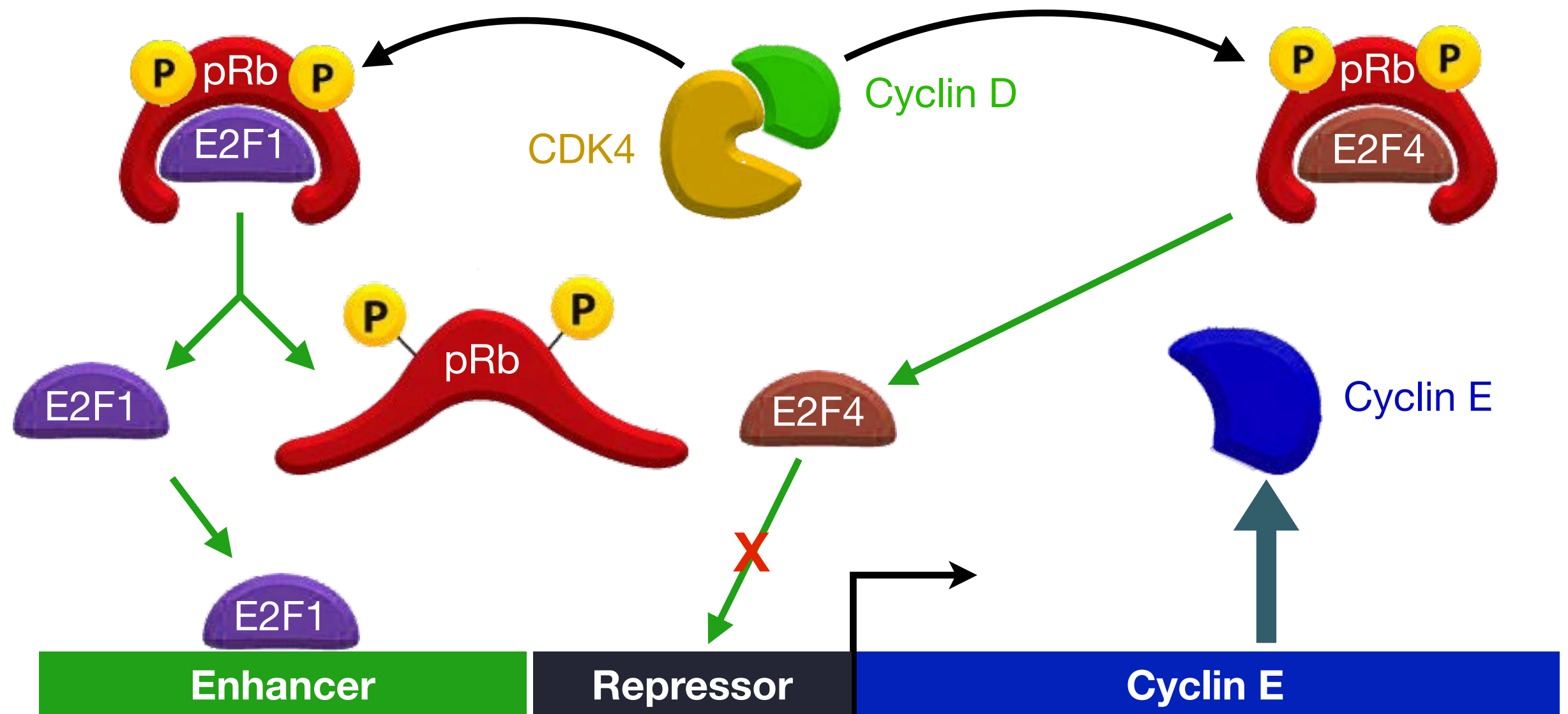
E2F proteins regulate expression of cyclin E.



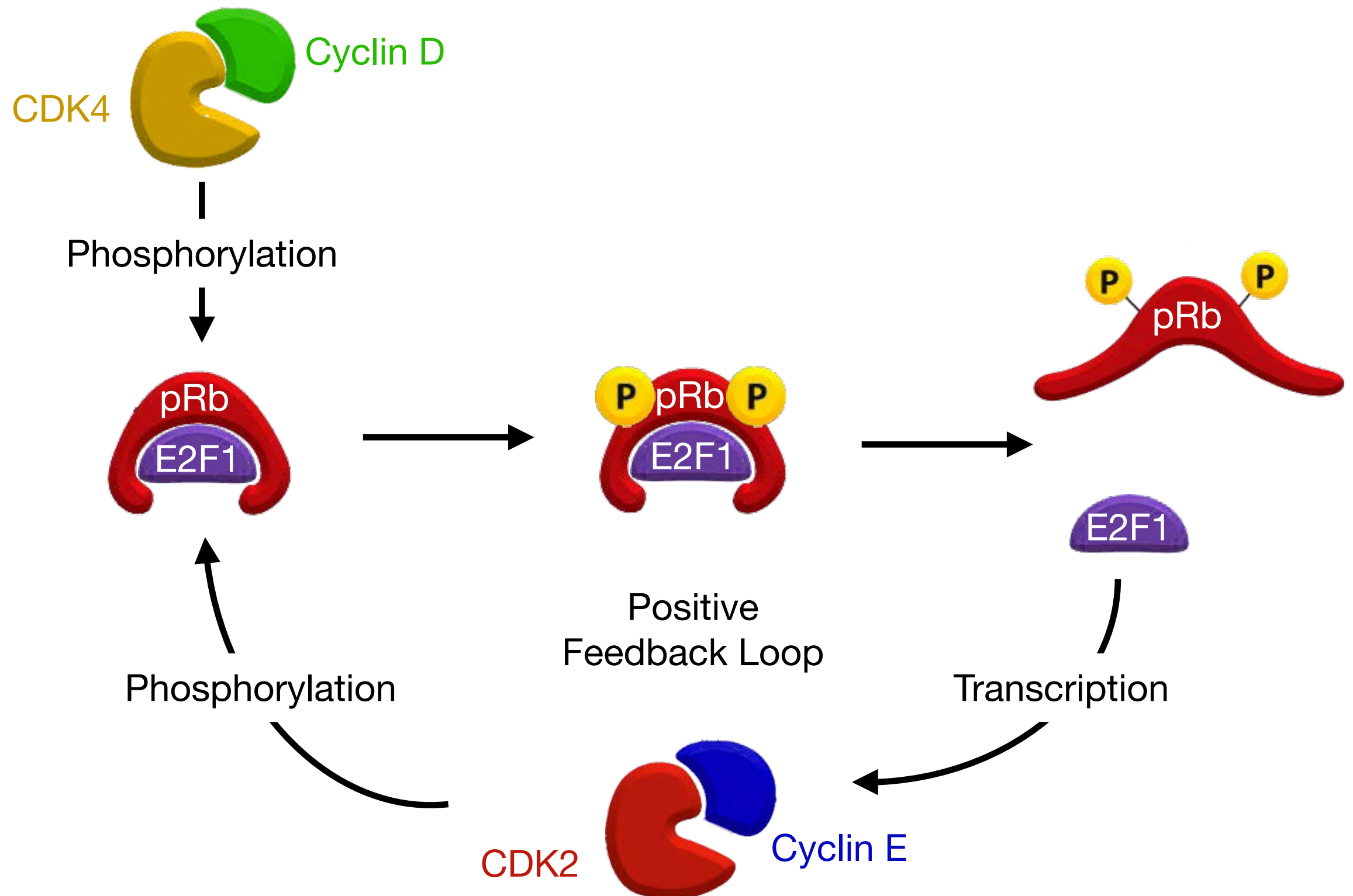
pRB inhibits cell division by promoting binding of E2F to repressor and inhibiting binding to



Cyclin D/CDK inactivate pRB to allow E2F to stimulate transcription of cyclin E.

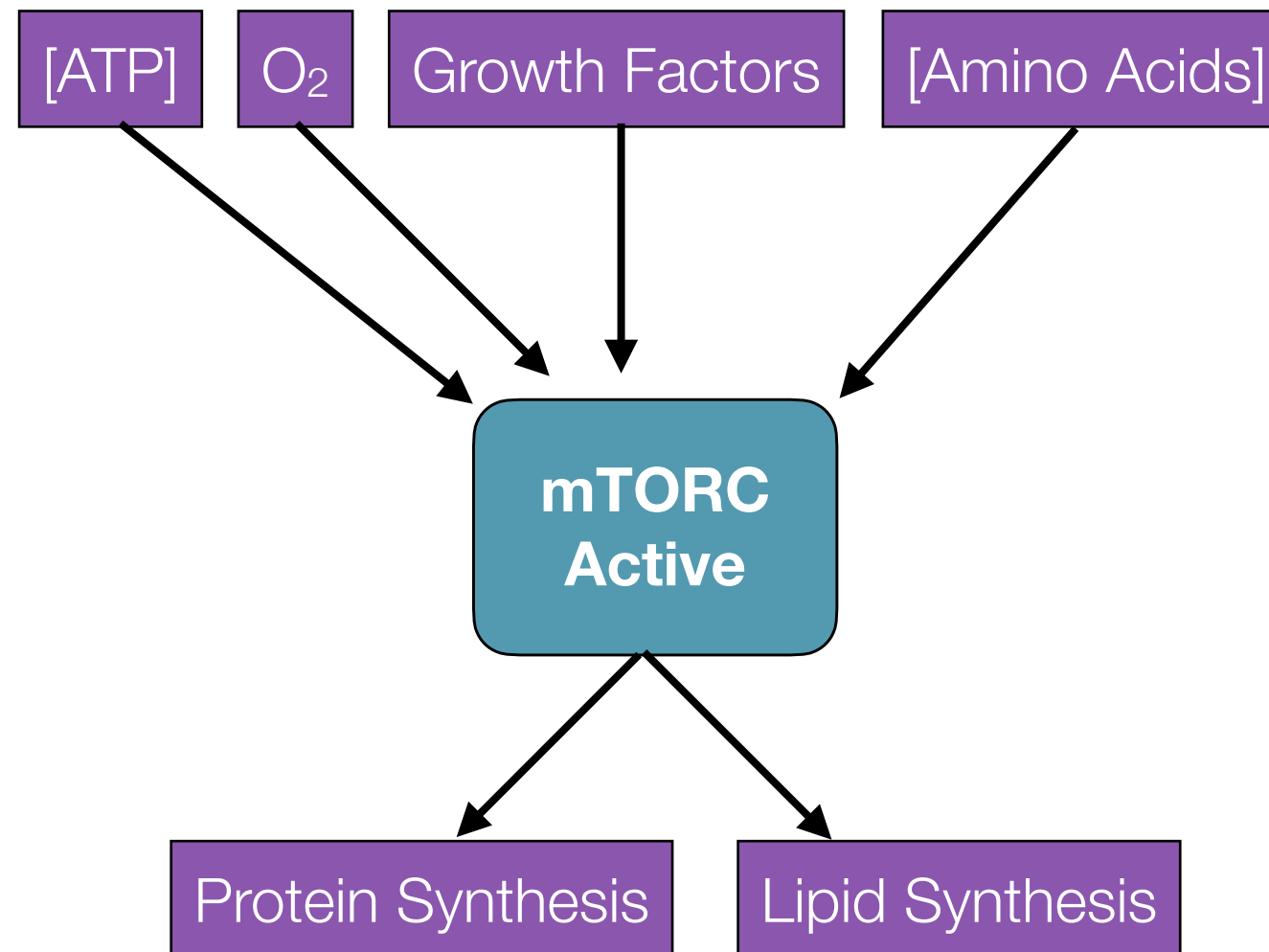


Positive feedback loop keeps cyclin E - CDK active.

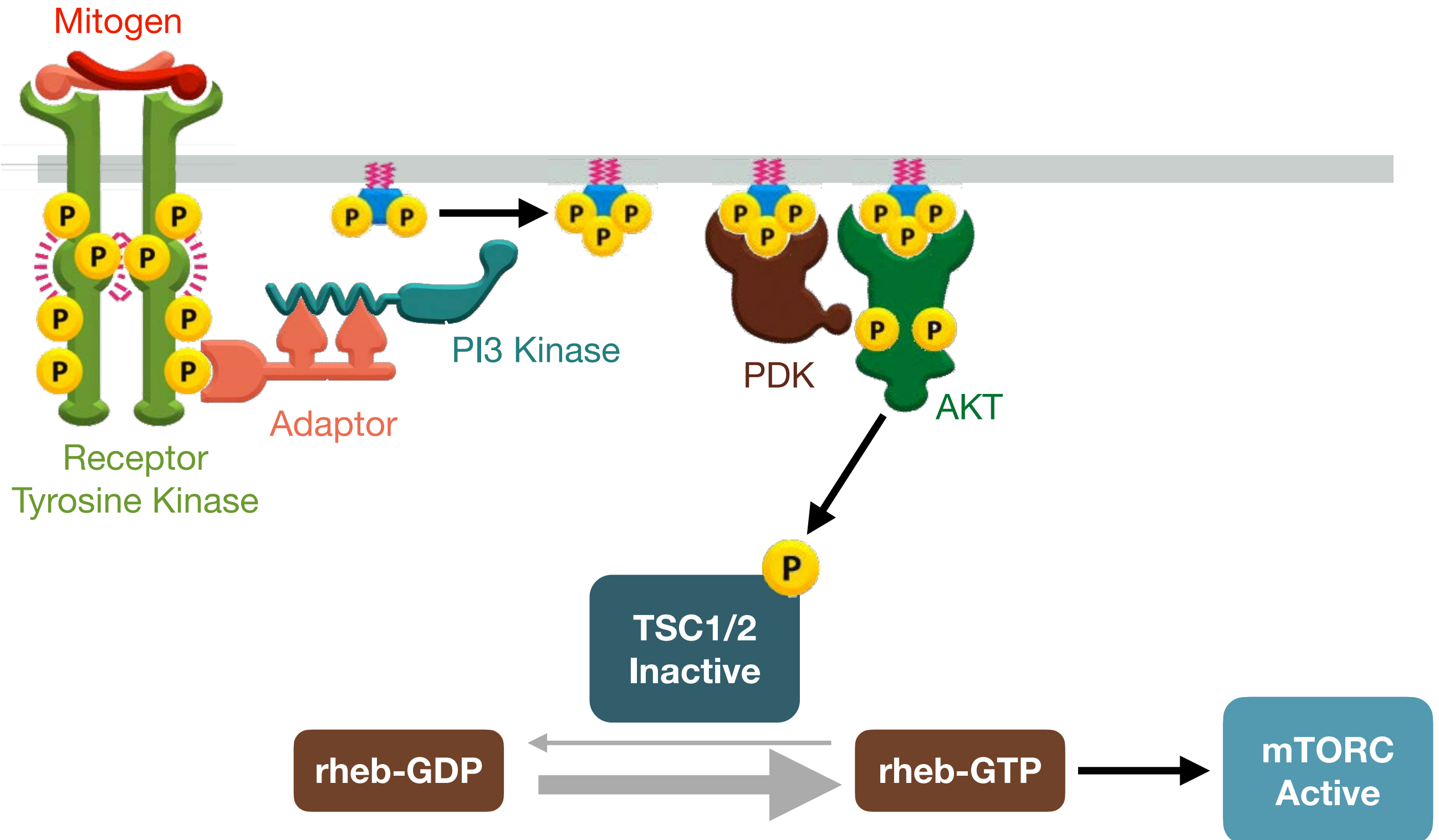


Mitogens and Increase in Cell Size

TOR complex integrates the nutritional status of the cell and regulates cell growth.

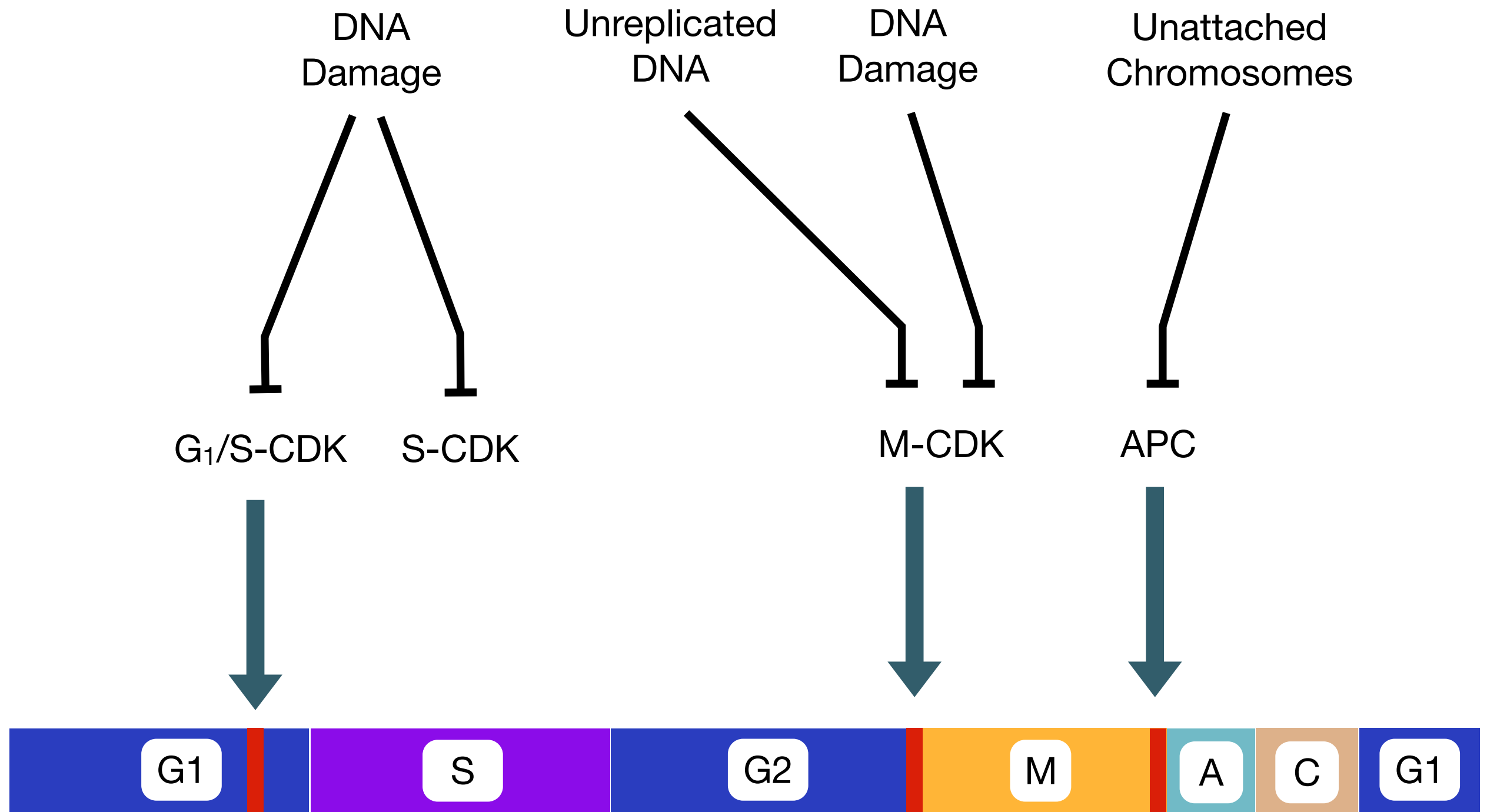


Mitogen-activated signaling pathways can turn on TOR complexes to promote cell growth.

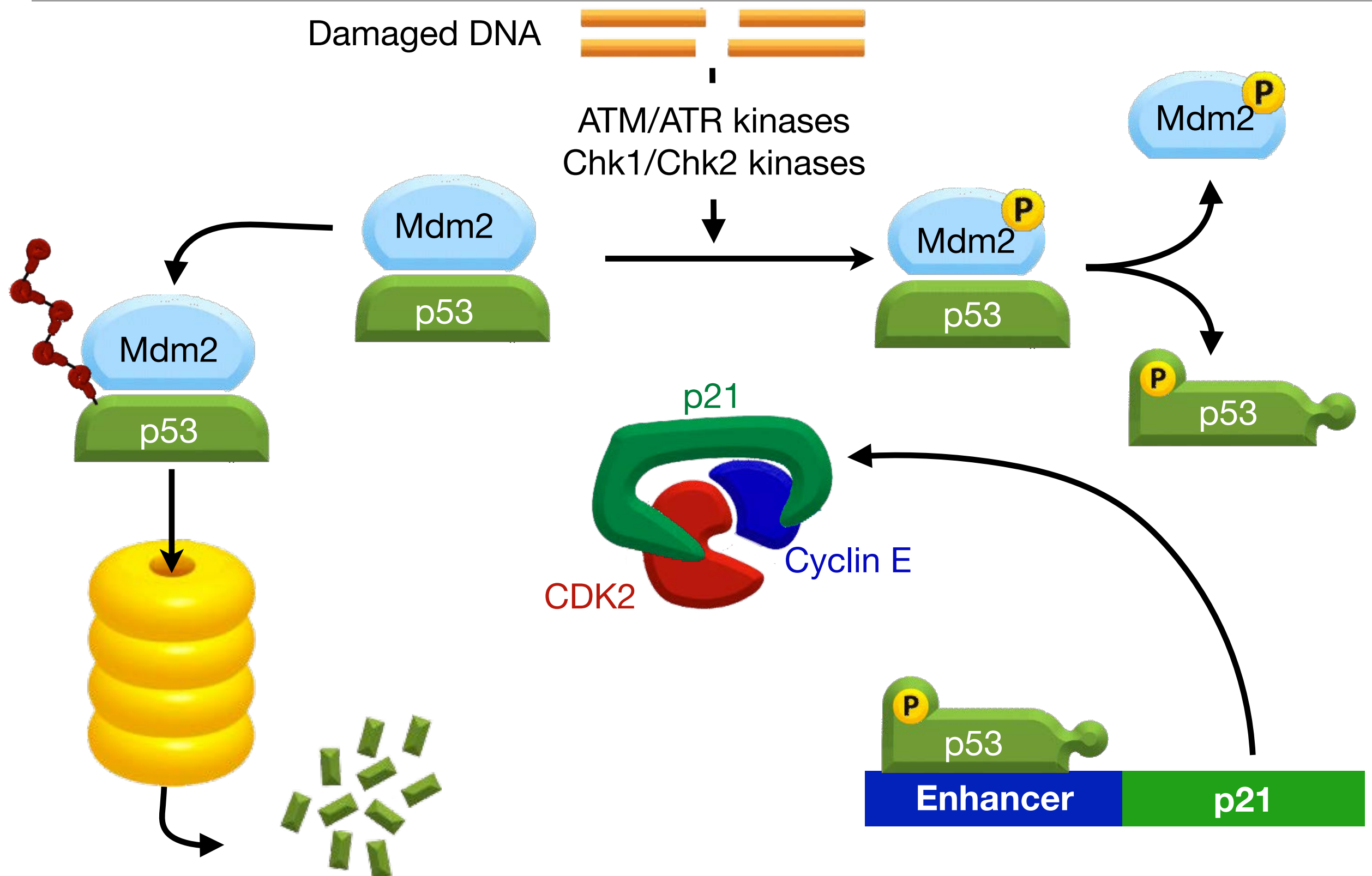


Checkpoints in the Cell Cycle

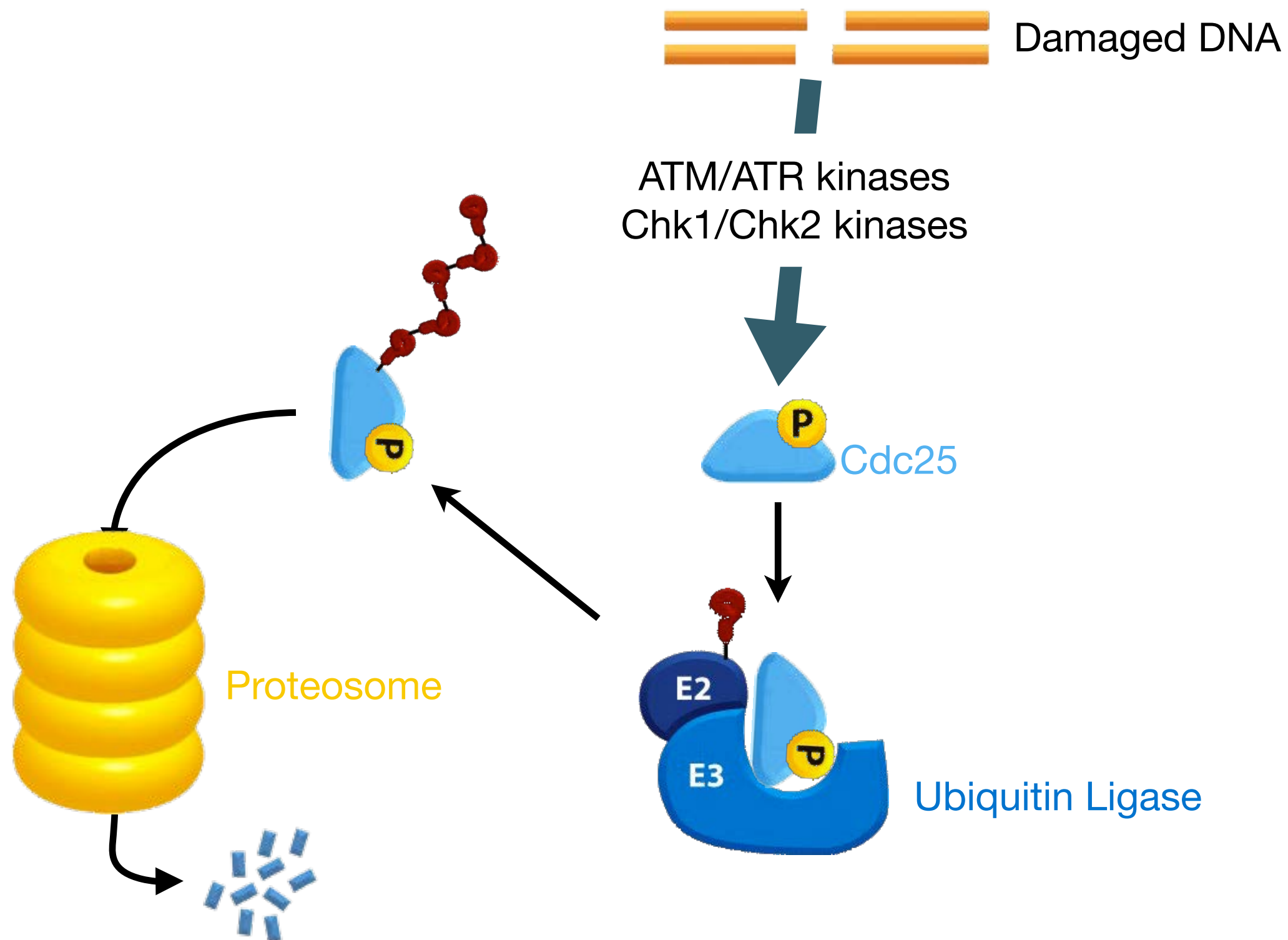
Checkpoints ensure completion of one stage of cell cycle before starting the next.



DNA damage activates p53 to arrest the cell cycle.

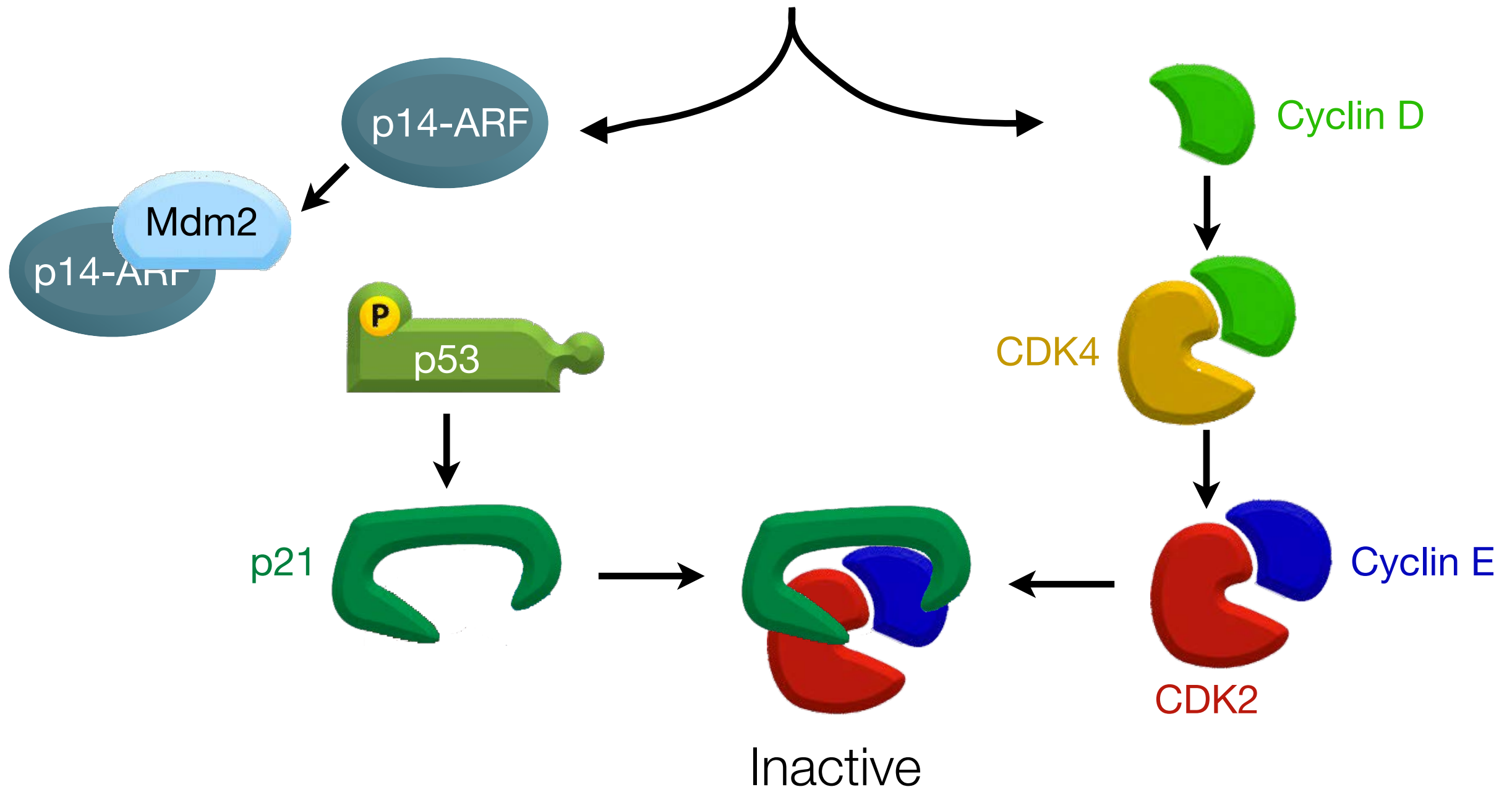


DNA damage also triggers degradation of Cdc25 to slow the cell cycle.

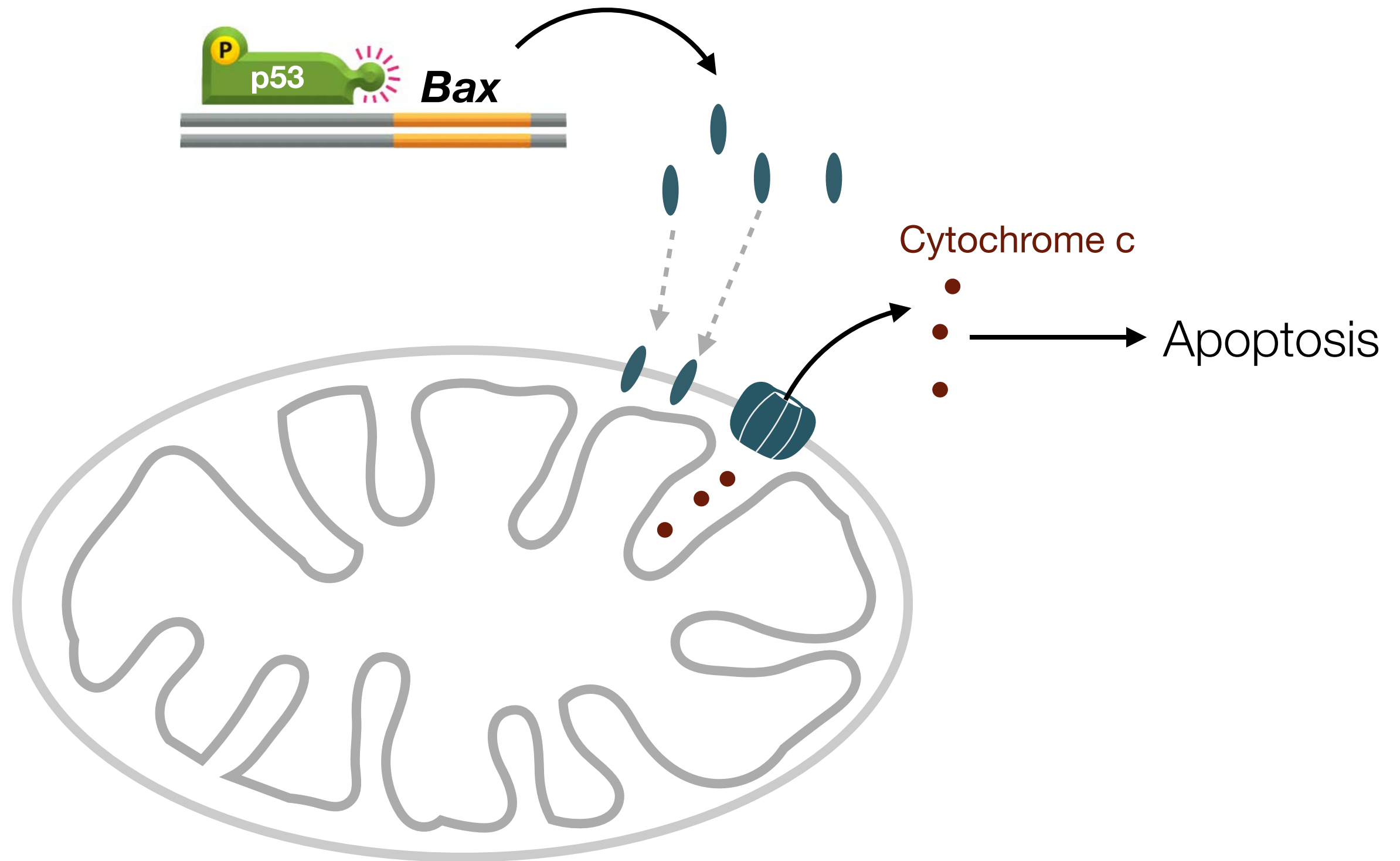


p53 is activated by oncogenes and slows cell division.

Oncogenic Transformation: Ras, Myc, E2F

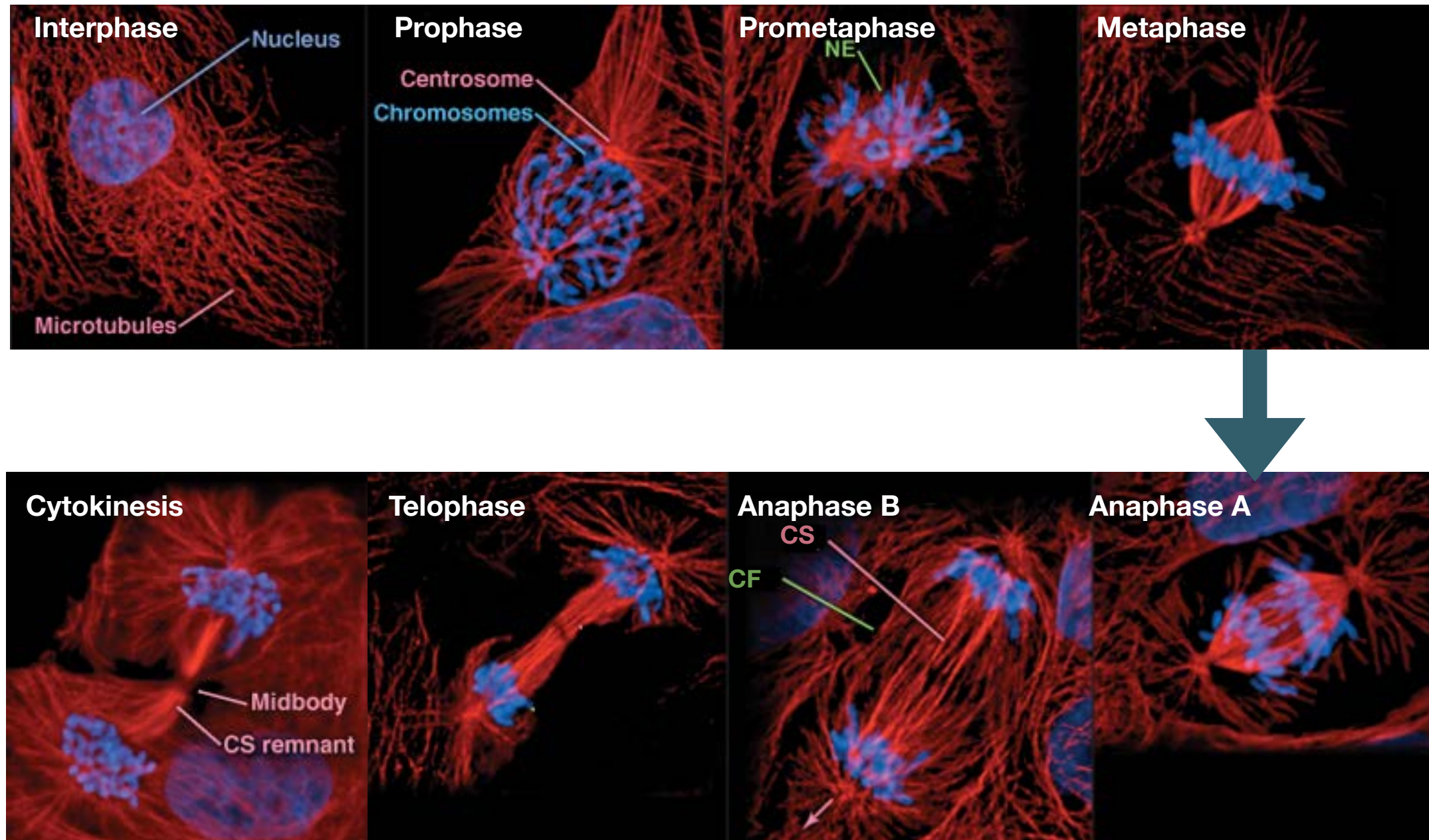


P53 triggers apoptosis by inducing release of cytochrome c from mitochondria.

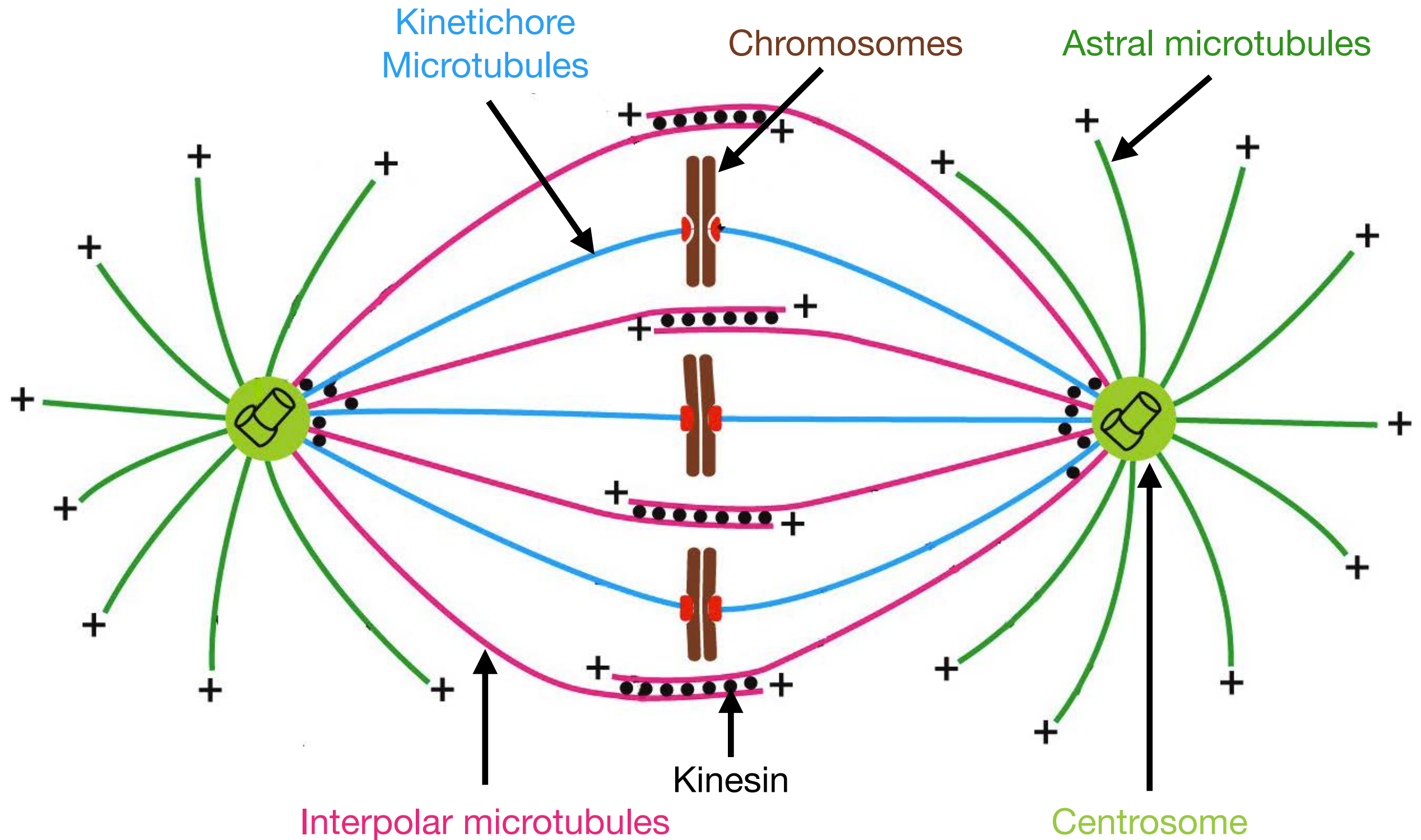


Mitosis

Mitosis proceeds in several defined stages that involve changes in microtubule organization.



Three types of microtubules comprise the mitotic spindle.

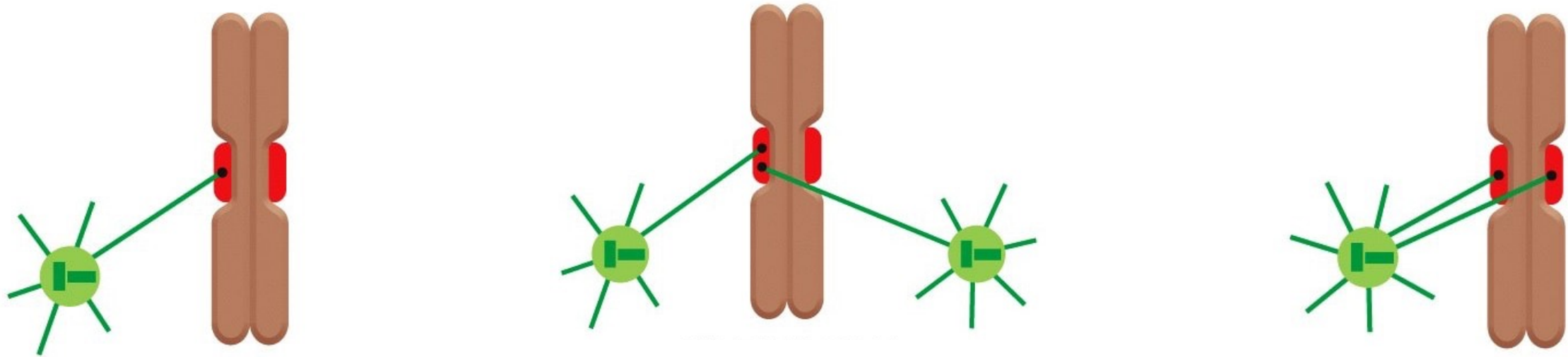


Mitotic Checkpoint

Incomplete or incorrect attachment of microtubules arrests cells in metaphase.

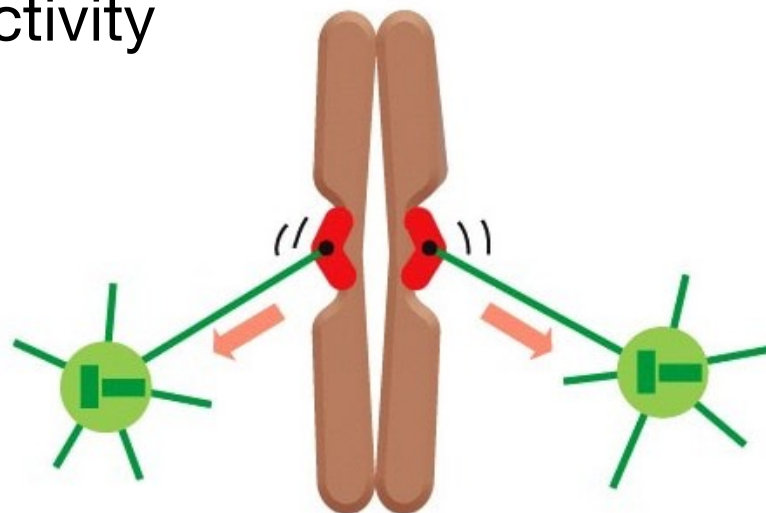
Metaphase Arrest

High cyclin B-CDK2 activity

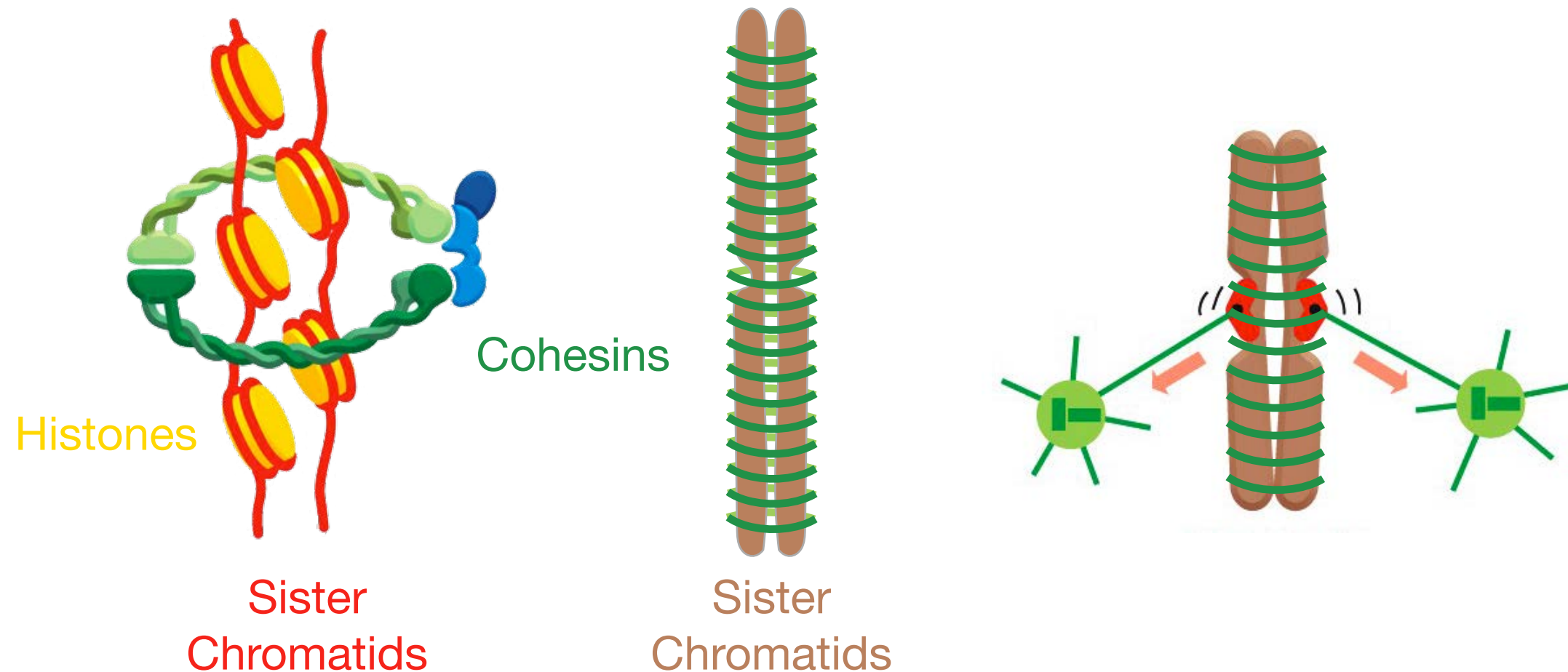


Transition to Anaphase

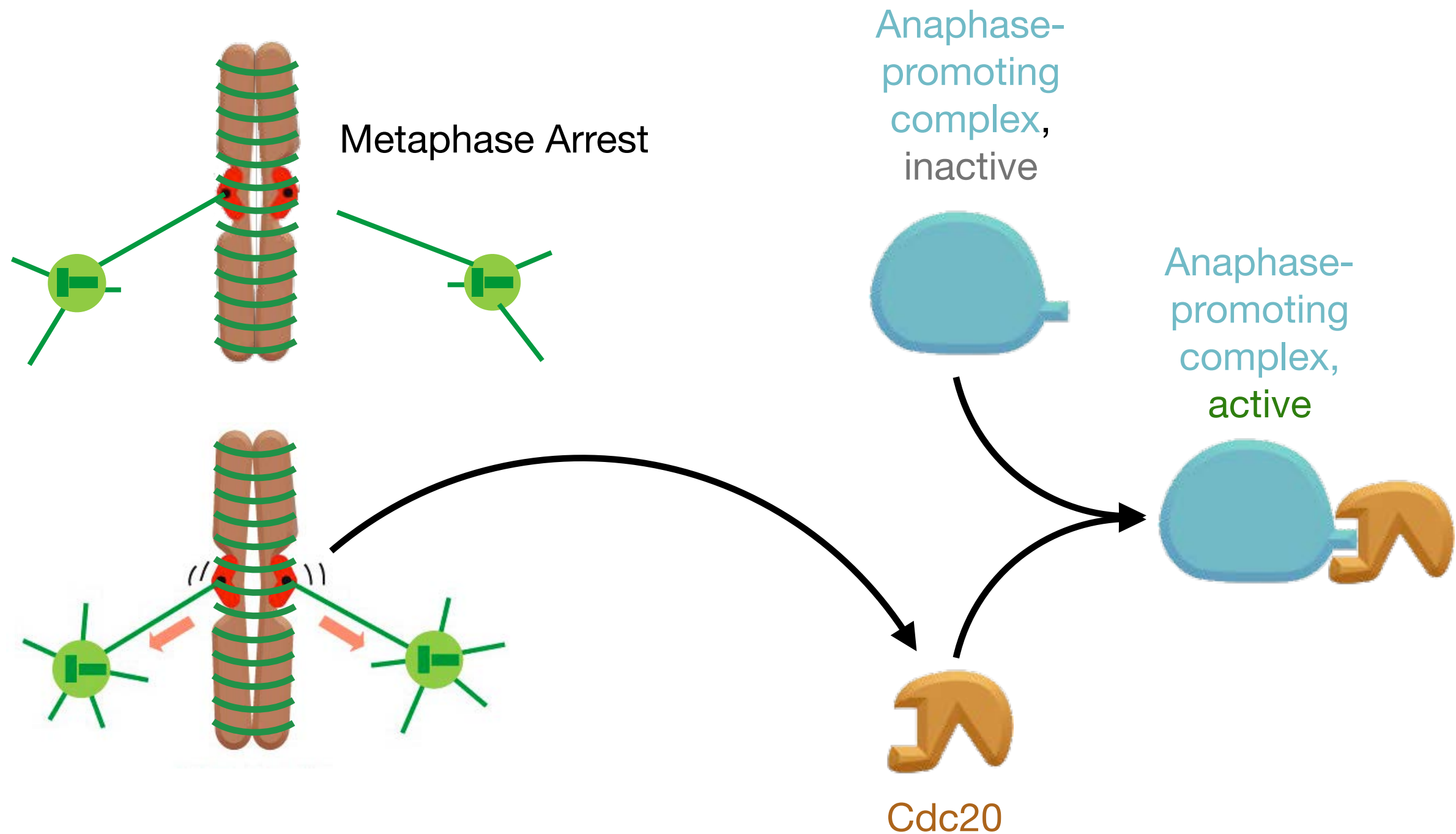
Decrease in cyclin B-CDK2 activity



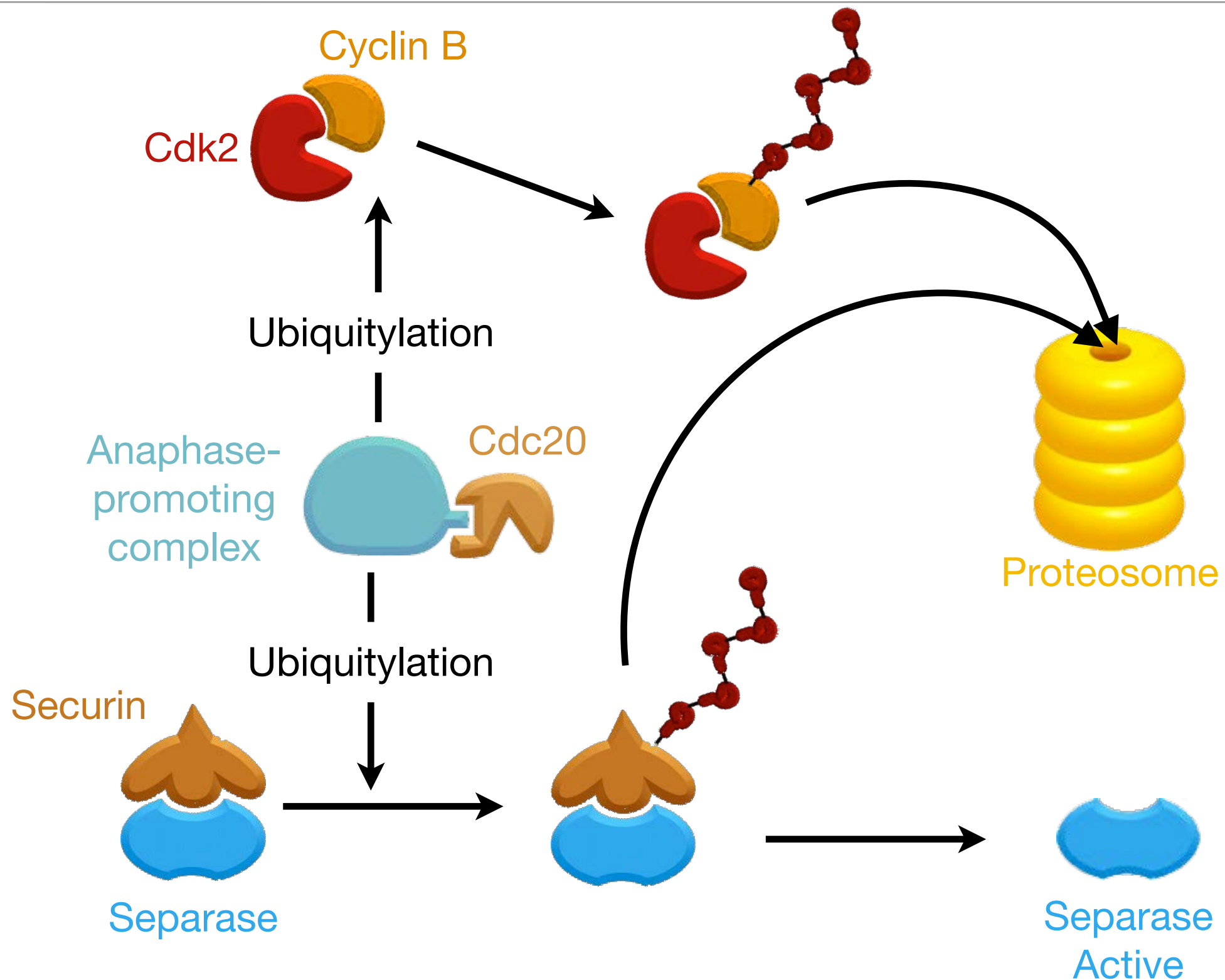
Cohesins tether sister chromatids to prevent premature separation.



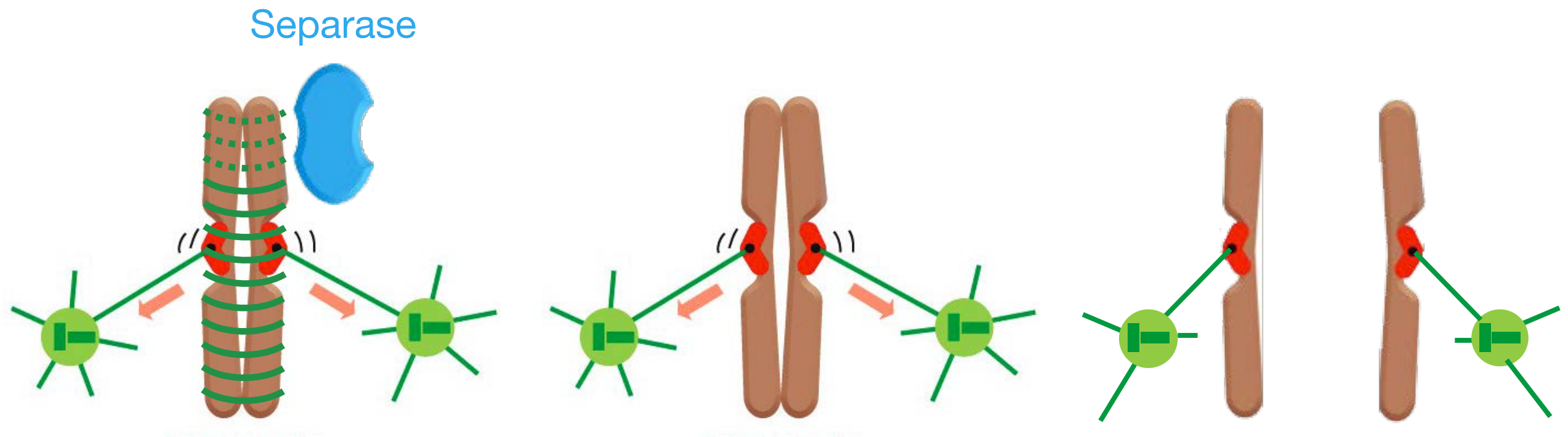
Unattached chromosomes prevent activation of anaphase promoting complex.



Anaphase-promoting complex ubiquitylates cyclin B and securin to trigger transition to anaphase.



Separase digests cohesins which allows tension from the spindle to separate chromosomes.



Take home points

- Cyclins and CDKs initiate different stages of the cell cycle
- Positive feedback is critical for commitment steps in the cell cycle
- Mitogens and anti-mitogens work through signaling pathways to influence the decision to divide
- Oncogenes trigger cell division in the absence of mitogen
- Tumor suppressors slow cell division by inactivating cyclin-CDKs
- Checkpoints monitor the state of the cell and can arrest the cell cycle