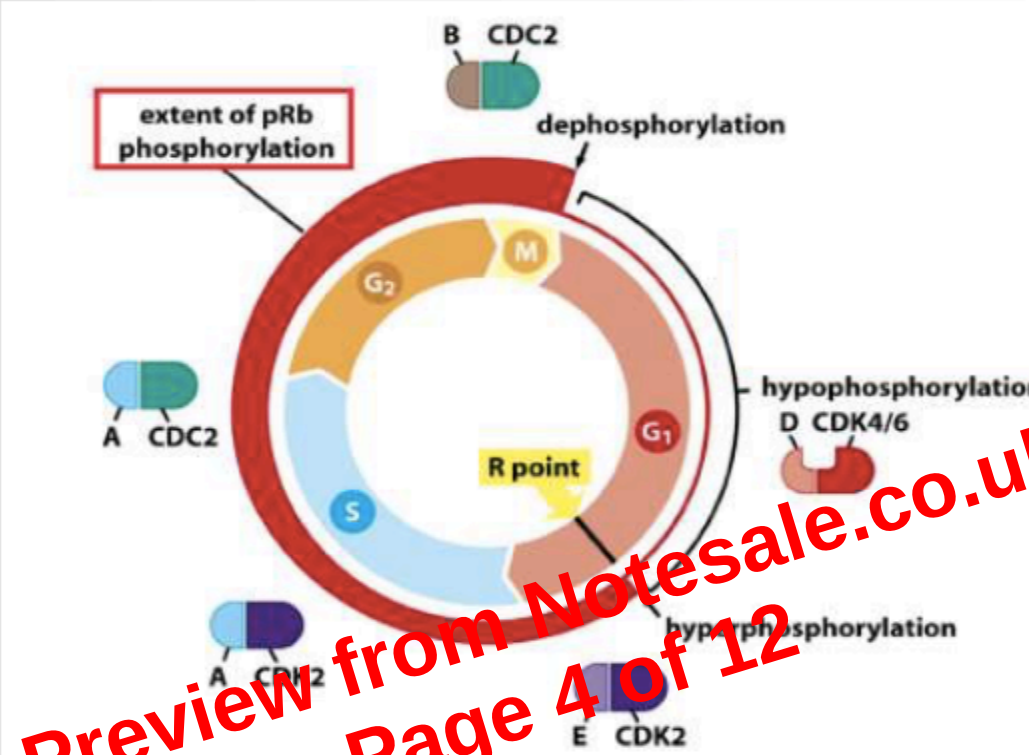
How does cyclin D drive passage through G1:

1. Cyclin D binds to CDK4 and CDK6 and the cyclin D/CDK4,6 are substrates for the Rb family, p107 and p130.
2. As well as acquisition of GF-independent, R-point passage involves biochemical modification of pRb.
3. That is, the degree of phosphorylation of Rb modulates whether or not the cell can progress through G1.

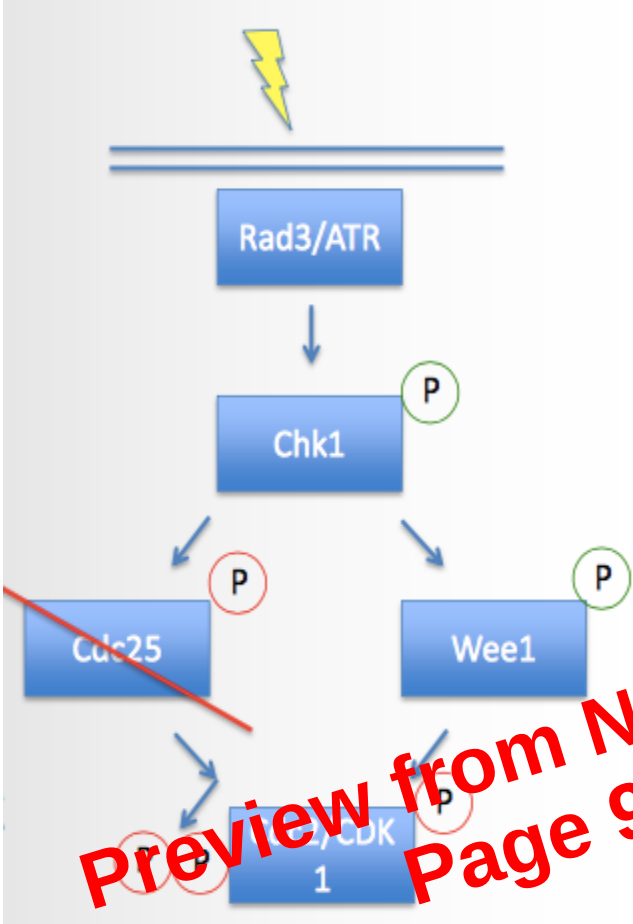


R point transition: **acquisition of growth factor-independence,** also accompanied by a biochemical alteration of pRb

Figure 8.19-20 *The Biology of Cancer* (© Garland Science 2007)

4. pRb binds a number of protein necessary for cell cycle progression via a conserved '**pocket' region**.
5. Phosphorylation of pRb releases these proteins, allowing cell cycle progression and one of the most important families of proteins bound and released by pRb are the **E2F family of TFs.**
6. This family drives expression of **S-phase genes,** in that, E2F bound by pRb inhibits the expression of S-phase genes, whereas inactive Rb allows E2F be activated and thus S-phase genes can be expressed.
7. These target genes also include cyclins for the next cell cycle phases and feed-forward mechanisms that ensure S-phase entry.
8. Furthermore, E2Fs bind to DNA as heterdimeric complexes with dimerization partners.

5. Cdc25A on the other hand is expressed in G1 in response to serum stimulation and is necessary for activating CDK2 for S-phase entry.
6. DNA damage or stalled replication forks are sensed by the kinases **ATM and ATR,** which phosphorylate the checkpoint kinases **CHK1 and CHK2.**
7. These kinases trigger cell cycle arrest and initiation of DNA repair processes.



a. CHK1-mediated phosphorylation of Cdc25 causes cdc25 to be ubiquinated and subject to proteasome-mediated degradation.
b. Inhibitory phosphatases on CDK1 are no longer removed and the cell **cannot** enter mitosis.
c. CHK1-mediated phosphorylation of Wee1 allows Wee1 to add inhibitory phosphorylation on CDK1, thus arresting the cell cycle in G2.

Rapid means of arresting the cell cycle without needing protein synthesis and is this **p53-independent.**

8. A similar **DNA-mediated cell cycle arrest can be achieved in G1** through ATM/ATR mediated inactivation of Cdc25A and subsequent failure to activate Cyclin E/CDK2.

CDC25 Phosphatases & Cancer:

1. The proto-oncogene, **c-Myc,** in partnership with **Max,** forms a transcription factor that can promote either oncogenic transformation or apoptosis.
2. This TF acts to enhance Cdc25A expression, and in turn this **cdc25A/B can cooperate with oncogenic Ras**, or loss of Rb, to transform primary mouse fibroblasts.
3. Cdc25 has been found to be overexpressed in a number of breast cancers, head and neck cancers and non-hodgkin's lymphomas.
4. Overall: cdc25 is a **proto-oncogene** because it can drive cell cycle progression.