12.3.1

Regulating molecules of the Cell Cycle

Molecules that help regulate the cell cycle can be categorized into two groups: positive and negative regulators. Positive regulating molecules help promote movement from one phase to another while negative regulators stop progression. This regulation can occur directly by the molecules themselves or indirectly through a plethora of other pathways.

Positive Regulators. Proteins called cyclins and cylcin-dependent kinases (Cdks) are considered positive cell cycle regulators and act by phosphorylating other proteins. Cyclins are activated in a very predictable manner throughout the cell cycle. The primary form of regulation occurs by altering the concentration of the cyclin/Cdk ratios. As cyclin concentrations fluctuate according to timing events in the cell cycle, different complexes of cyclin/Cdk complexes form which result in different phosphorylation activities. It is the amount and activity of the cyclin/Cdk activities that signal the cell to continue to different phases.

Negative Regulators. There are three negative regulating proteins called retinoblastoma protein (Rb), p53, and p21. These proteins act primarily at the G1 checkpoint. P53 identifies damaged DNA and then stops the cycle and recruits repairing enzymes. If the damage is too extensive, P53 will instead start process that will lead to cell death called **apoptosis**. As the levels of p53 increase, p21 becomes triggered which reinforces the stopping of the cell cycle by inhibiting cyclin/Cdk complexes. The Rb protein monitors cell size because its activity is link to the cell growth. As cell size increases, the Rb protein becomes phosphorylated which inactivates it. When Rb is dephosphorylated, it is active and binds to and inhibits transcription factors. Transcription factors turn on specific genes allowing the production of proteins associated with the gene so if growth is going to continue the negative regulators must not be active.