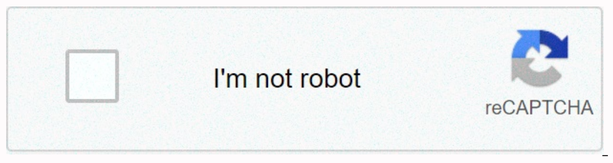

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How is the cell cycle regulated by cyclins

By the end of this section, you will be able to: Understand how the cell cycle is controlled by both internal and external cell mechanisms Explain how the three internal control points appear at the end of G1, at the G2/M transition, and during metaphase Describe the molecules that control the cell cycle through positive and negative regulation The length of the cell cycle is very variable, even in the cells of a single organism. In humans, the frequency of cell turnover varies from a few hours in early embryonic development, to an average of two to five days for epithelial cells, and to a lifetime of man spent in G0 specialized cells, such as cortical neurons or cardiac muscle cells. There are also variations in the time that a cell spends in each phase of the cell cycle. When the cells of fast-dividing mammals are grown in culture (outside the body under optimal growing conditions), the cycle duration is about 24 hours. In human cells that are rapidly divided with a 24-hour cell cycle, phase G1 lasts about nine hours, phase S lasts 10 hours, phase G2 lasts about four and a half hours, and phase M lasts about half an hour. In the first fruit bite embryos, the cell cycle ends in about eight minutes. The timing of events in the cell cycle is controlled by mechanisms that are both internal and external to the cell. Adjustment of the cell cycle by external events Both initiation and inhibition of cell division are triggered by external cell events when the replication process is about to begin. An event can be as simple as the death of a nearby cell or as crushing as the release of growth-promoting hormones, would be human growth hormone (HGH). A lack of HGH can inhibit cell division, resulting in nanisms, while too much HGH can lead to gigantism. Cell agglomeration can also inhibit cell division. Another factor that can initiate cell division is cell size; as a cell grows, it becomes ineffective due to the decreasing surface-volume ratio. The solution to this problem is to divide. Whatever the source of the message, the cell receives the signal, and a series of events inside the cell allows it to enter the interphase. Going further from this initiation point, each parameter required during each phase of the cell cycle must be observed or the cycle cannot progress. Regulation at internal checkpoints It is essential that the daughter cells produced are accurate duplicates of the parent cell. Mistakes in duplicating or distribution of chromosomes lead to mutations that can be transmitted to each new cell produced from an abnormal cell. To a compromised cell to continue to divide, there are internal control mechanisms operating at three control points of the main cell cycle. A checkpoint is one of several points in the eukaryotic cell cycle at which a cell at the next stage of the cycle can be stopped until conditions are favourable. These checkpoints appear near the end of G1, at the G2/M transition and during metaphase (Figure 1). Figure 1. The cell cycle is controlled at three checkpoints. DNA integrity is assessed at the G1 checkpoint. Proper chromosome duplication is assessed at control point G2. The fixation of each kinetochore to an axis fibre shall be assessed at control point M. Control point G1 Control point G1 determines whether all conditions are favourable for cell division to continue. The G1 checkpoint, also called the restriction point (in yeast), is a point at which the cell engages irreversibly in the process of cell division. External influences, such as growth factors, play an important role in transporting the cell beyond the G1 checkpoint. In addition to adequate reserves and cell size, there is a control for damage to genomic DNA at the G1 control point. A cell that does not meet all requirements will not be allowed to progress to phase S. The cell can stop the cycle and try to fix the problematic state, or the cell can advance to G0 and wait for additional signals when conditions improve. The G2 control point The G2 control point shall be in the mitotic phase if certain conditions are not met. As at control point G1, cell size and protein reserves shall be assessed. However, the most important role of the G2 control point is to ensure that all chromosomes have been replicated and that the DNA reproduced is not damaged. If the control mechanisms detect problems with dna, the cell cycle is stopped, and the cell tries to either complete the DNA reproduction or repair the damaged DNA. Control point M Control point M takes place near the end of the metaphase stage of cariokinesia. The M control point is also known as the axis control point because it determines whether all sister chromatids are correctly attached to the axis microtubules. Since the separation of sister chromatids during anaphasis is an irreversible step, the cycle will not continue until the kinetocores of each pair of sister chromatids are firmly anchored to at least two axis fibers resulting from the cell's opposite poles. Cell cycle regulatory molecules In addition to internally controlled control points, there are two groups of intracellular molecules that regulate the cell cycle. These regulatory molecules either promote cell progress to the next phase (positive adjustment) or stop the cycle (negative adjustment). Regulatory molecules may act individually or influence the activity or production of other regulatory proteins. Therefore, the failure single regulator can have almost no effect on the cell cycle, especially if more than one mechanism controls the same event. On the other hand, the effect of a weak or non-functioning regulatory authority may be fatal to the cell if multiple processes are affected. Positive cell cycle regulation Two protein groups, called cyclines and cycline-dependent kinases (Cdks), are responsible for cell progress through different control points. Levels of the four cycline proteins fluctuate throughout the cell cycle in a predictable pattern (Figure 2). The increase in the concentration of cycline proteins is triggered by both external and internal signals. After the cell moves to the next stage of the cell cycle, the cyclines that were active in the previous stage are degraded. Figure 2. The concentrations of cycline proteins change throughout the cell cycle. There is a direct correlation between the accumulation of cycline and the three major control points of the cell cycle. Also note the sharp decrease in cycline levels after each control point (transition between cell cycle phases), as cycline is degraded by cytoplasmic enzymes. (credit: changes to work by WikiMiMa/Wikimedia Commons) Figure 3. Cycline-dependent kinases (Cdks) are kinase proteins that, when fully activated, can phosphorylate and thus activate other proteins that advance the cell cycle beyond a control point. To become fully activated, a Cdk must bind to a cycline protein and then be phosphorylated by another kinase. Cyclins regulate the cell cycle only when they are closely related to the Cdks. Like all kinases, Cdks are enzymes (kinases) that phosphorylate other proteins. Phosphorylation activates the protein by changing its shape. The phosphorylated proteins of Cdks are involved in the cell's advancement to the next phase. (Figure 3). Cdk protein levels are relatively stable throughout the cell cycle; however, cycline concentrations fluctuate and determine when Cdk/cycline complexes are formed. Different cyclines and Cdks bind to certain points in the cell cycle and thus regulate different checkpoints. Because cyclic fluctuations in cycline levels are based on the cell cycle calendar and not on specific events, cell cycle regulation usually occurs either through the cdk molecules or the cdk/cycline complexes. Without a specific concentration of fully activated cycline/Cdk complexes, the cell cycle cannot pass through the control points. Although cyclines are the main regulatory molecules that determine the forward impulse of the cell cycle, there are several other mechanisms that adjust the progress of the cycle with negative rather than positive effects. These mechanisms essentially block the progression of the cell cycle until problematic conditions are resolved. Molecules that prevent cdks are called cdk inhibitors. Many of these inhibitor molecules directly or indirectly monitor a particular cell cycle event. The block placed on the Cdks of molecules will not be removed until the specific event in which the inhibitor monitors are completed. Negative cell cycle regulation The second group of cell cycle regulatory molecules are negative regulators. Negative controllers shut down the cell cycle. Remember that in positive regulation, active molecules cause the cycle to progress. The best understood regulatory negative molecules are the protein retinoblastoma (Rb), p53, and p21. Retinoblastoma proteins are a group of tumor suppressor proteins common in many cells. Names 53 and 21 refer to the functional molecular masses of proteins (p) in kilodaltons. Much of what is known about cell cycle regulation comes from research conducted with cells that have lost regulatory control. All three of these regulatory proteins were found to be damaged or non-functional in cells that began to reproduce uncontrollably (became cancerous). In each case, the root cause of uncontrolled progress through the cell cycle was a defective copy of the regulatory protein. Rb, p53 and p21 act mainly at control point G1. p53 is a multifunctional protein that has a major impact on a cell's commitment to division, as it acts when there is damaged DNA in cells that are subjected to preparatory processes during G1. If damaged DNA is detected, p53 stops the cell cycle and recruits enzymes to repair DNA. If the DNA cannot be repaired, p53 can trigger apoptosis, or cell suicide, to prevent duplication of damaged chromosomes. As p53 levels increase, p21 production is triggered. p21 requires stopping the cycle dictated by p53 by binding and inhibiting the activity of Cdk/cyclin complexes. As a cell is exposed to more stress, higher levels of p53 and p21 accumulate, making it less likely that the cell will move into phase S. Rb exerts its regulatory influence on other positive regulatory proteins. Mainly, Rb monitors cell size. In the active, dephosphorylated state, Rb binds to proteins called transcription factors, most commonly, E2F (Figure 4). Transcription factors activate specific genes, allowing the production of proteins encoded by that gene. When Rb is linked to E2F, the production of protein needed for the G1/S transition is blocked. As the cell grows in size, Rb is slowly phosphorylated until it becomes inactivated. Rb releases E2F, which can now activate the gene that produces the transitional protein, and this particular block is removed. For the cell to pass each checkpoint, all positive regulators must be switched on and all negative regulators must be switched off. Figure 4. Rb cell cycle and releases its retention in response to cell growth. Rb and other proteins that negatively regulate the cell cycle are sometimes called tumor suppressors. Why do you think the name tumor suppressor might be suitable for these proteins? Protein? Summary Each stage of the cell cycle is monitored by internal controls called checkpoints. There are three major control points in the cell cycle: one near the end of G1, a second at the G2/M transition and the third during metaphase. Positive regulator molecules allow the cell cycle to advance to the next stage. Negative regulator molecules monitor cellular conditions and can stop the cycle until specific requirements are met. 1. Rb and other proteins that negatively regulate the cell cycle are sometimes called tumor suppressors. Why do you think the name tumor suppressor might be a suitable for these proteins? 2. Describe the general conditions to be met at each of the three control points of the main cell cycle. 3. Explain the roles of positive cell cycle controllers compared to negative regulators. 4. What steps are needed for Cdk to become fully active? 5. Rb is a negative regulator that blocks the cell cycle at the G1 checkpoint until the cell reaches a required size. What molecular mechanism does Rb use to stop the cell cycle? 1. Rb and other negative regulatory proteins control cell division and therefore prevent the formation of tumors. Mutations that prevent these proteins from performing their function can lead to cancer. 2. The G1 control point shall monitor the proper growth of cells, the state of genomic DNA, adequate energy deposits and materials for phase S. At control point G2, DNA is checked to ensure that all chromosomes have been duplicated and that there are no mistakes in newly synthesized DNA. In addition, cell size and energy reserves are evaluated. The M control point confirms the correct fixation of the mitotic axis fibers at the kinetochore. 3. Positive cell regulators, would be cycline and Cdk perform tasks that advance the cell cycle to the next stage. Negative regulators such as Rb, p53 and p21 block cell cycle progression until certain events occur. 4. Cdk must bind to a cycline and must be phosphorylated in the correct position in order to become fully active. 5. Rb is active when it is dephosphorus. In this state, Rb binds to E2F, which is a transcription factor necessary for the transcription and eventual translation of the molecules needed for the Transition G1/S. E2F cannot transcribe certain genes when bound to Rb. As the cell grows in size, Rb becomes phosphorylate, inactivated and releases E2F. E2F can then promote the transcription of the genes it controls, and transition proteins will be produced. cell cycle control point: a mechanism that monitors the preparation of a eukaryotic cell to advance through the different stages of the cycle cycline: one in a group of which works together with cycline-dependent kinases to help regulate the cell cycle by phosphorylation of key proteins; cycline concentrations fluctuate throughout the cycline-dependent cell cycle one of a group of kinase proteins that helps regulate the cell cycle when it is bound to cycline; works for phosphorylated other proteins that are either activated or inactivated by phosphorylation p21: cell cycle regulatory protein that inhibits the cell cycle; its levels are controlled by p53 p53: the cell cycle regulatory protein that regulates cell growth and monitors DNA damage; stops cell cycle progression in cases of DNA damage and may induce retinoblastoma apoptosis (Rb): regulatory molecule that has negative effects on the cell cycle by interacting with a transcription factor (E2F) (E2F)

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