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Correction mechanism of tumor suppressor gene p53 on abnormal cell G1/S phase transition

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Abstract:

This article aims to delve into the correction mechanism of the tumor suppressor gene p53 on abnormal cell G1/S phase transition. As an important tumor suppressor gene, p53 plays a crucial role in maintaining normal cell growth and preventing carcinogenesis. Through a comprehensive analysis of relevant research, this paper elucidates the monitoring and regulatory role of p53 in the cell G1/S phase transition process, as well as the specific mechanisms by which it corrects abnormalities in the G1/S phase transition through various downstream effector molecules and signaling pathways. This provides a theoretical foundation for a deeper understanding of cell cycle regulation and the molecular mechanisms underlying tumor development.

Keywords:

p53 gene
Cell cycle
G1/S phase transition
Correction mechanism

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1. Introduction

The normal progression of the cell cycle is essential for maintaining cell growth, differentiation, and the homeostasis of tissues and organs. The G1/S phase transition is a critical checkpoint in the cell cycle, determining whether cells enter the DNA synthesis phase for replication. During this process, multiple genes and signaling pathways work together to ensure that cells divide and proliferate under appropriate conditions. The tumor suppressor gene p53, as a key regulator of the cell cycle, can monitor various abnormal signals within cells and correct abnormalities in the cell cycle process through multiple mechanisms, especially playing an irreplaceable role in correcting abnormalities in the G1/S phase transition.

2. Overview of the p53 Gene

The tumor suppressor p53 participates in the transcriptional regulation of multiple genes as a trans-acting factor, exerting cell cycle arrest and promoting apoptosis during stress such as DNA damage [1]. The p53 gene is located in the p13 region of human chromosome 17, and the encoded p53 protein is a transcription factor with a molecular weight of 53 kDa. Under normal circumstances, the p53 protein is maintained at a low

level in cells, but its expression and activity rapidly increase when cells are subjected to various stress stimuli such as DNA damage, oncogene activation, hypoxia, or nutritional deficiency. The p53 protein contains multiple functional domains, including an N-terminal transcriptional activation domain, a proline-rich growth inhibitory domain, a sequence-specific DNA binding domain, a nuclear localization signal, a tetramer oligomerization domain, and a C-terminal non-specific DNA regulatory domain. These functional domains work together to enable p53 to perform its various biological functions, such as cell cycle arrest, induction of apoptosis, promotion of DNA repair, and maintenance of genomic stability.

3. Monitoring Mechanism of p53 on Cell G1/S Transition

The precise regulation of cell cycle progression is crucial for maintaining normal physiological functions and genomic stability of cells. The G1/S transition, as a key checkpoint, relies on a strict monitoring mechanism for its normal progression. This chapter focuses on the role of the tumor suppressor gene p53 in monitoring the G1/S transition of cells. It elaborates on how p53 sensitively perceives various abnormal signals within cells from three dimensions: DNA damage monitoring, oncogene activation monitoring, and cellular metabolic state monitoring, to ensure the orderly progression of the cell cycle and maintain the healthy state of cells.

3.1 DNA Damage Monitoring

In cellular activities, many factors can cause DNA damage, such as ultraviolet radiation, ionizing radiation, and chemical carcinogens, resulting in DNA double-strand breaks or base damage. At this time, kinases such as ATM and ATR within the cell act as DNA damage sensor proteins and are activated to phosphorylate the p53 protein [2]. This not only enhances the stability of the p53 protein and activates its transcriptional activity, but the p53 protein can also directly bind to damaged DNA, strengthening the effectiveness of damage monitoring. This allows for precise control of the cell's response to DNA damage.

3.2 Oncogene Activation Detection

Within cells, the activation of oncogenes such as Ras and Myc can disrupt cellular signaling pathways and cause uncontrolled cell proliferation. p53 plays a key role in this process as it can sensitively detect abnormal signals generated by oncogene activation. By directly binding to oncogene proteins or interacting with downstream signaling molecules, p53 precisely regulates its own activity, thereby inhibiting excessive cell proliferation. This effectively prevents abnormal transition from G1 to S phase and maintains the normal order of the cell cycle.

3.3 Cellular Metabolic State Monitoring

The cellular metabolic state is closely linked to the progression of the cell cycle, and p53 plays a crucial role in monitoring it. p53 can accurately sense the level of nutrients within the cell and whether the energy metabolism state is normal [3]. Once the cell experiences a shortage of nutrients or metabolic disorders, p53 is rapidly activated. It then regulates the expression and activity of metabolic enzymes related to glucose metabolism and mitochondrial function, altering the cell's energy acquisition method. This keeps the cell cycle in the G1 phase, preventing DNA synthesis under adverse conditions and maintaining the stability of the cell genome.

4. Correction Mechanisms of p53 for Abnormal G1/S Transition in Cells

The G1/S transition process in cells is like a precisely operating clock, and any abnormalities can have a significant impact on the fate of the cell. This chapter focuses on the correction mechanisms of the tumor suppressor gene p53 in this context. From transcriptional activation of the p21 gene to block the cell cycle, to inducing apoptosis to eliminate irreparable abnormal cells, and promoting DNA repair to restore genomic stability, p53 strives to maintain the normal rhythm of the cell cycle through its multi-dimensional regulatory strategies, avoiding abnormal cell proliferation such as canceration.

4.1 Transcriptional Activation of the p21 Gene

p21 is one of the important downstream target genes

of p53, and its encoded p21 protein is a cyclin-dependent kinase inhibitor (CKI). Activation of p53 can transcriptionally activate the expression of the p21 gene, increasing the level of p21 protein. The p21 protein can bind to cyclin-CDK complexes, such as cyclin D-CDK4/6 and cyclin E-CDK2, inhibiting their kinase activity. This results in the inability of cyclins to phosphorylate the retinoblastoma protein (Rb) [4]. In its non-phosphorylated state, Rb maintains its binding to the transcription factor E2F, preventing E2F activation. This inhibits the transcription of genes related to DNA replication, causing cell cycle arrest in the G1 phase and preventing abnormal cell entry into the S phase.

4.2 Induction of Apoptosis

The G1/S phase is a critical turning point in the cell cycle process. Once the transition at this stage becomes abnormal, and the DNA damage suffered cannot be restored to normal through repair mechanisms, the p53 gene quickly activates its key role. Through precise molecular regulatory mechanisms, it actively transcriptionally activates a series of apoptosis-promoting genes such as Bax, Puma, and Noxa, while inhibiting the expression of anti-apoptotic genes such as Bcl-2 and Bcl-xL [5]. This bidirectional and precise gene regulation successfully activates intracellular apoptotic signaling pathways, causing abnormal cells with serious problems to undergo apoptosis. This effectively prevents their uncontrolled proliferation and cancerous trends, ensuring the stability of the cell's internal environment and providing a basic guarantee for the healthy operation of the entire organism.

4.3 Promotion of DNA Repair

For DNA damage that occurs during the G1/S transition, p53 can also correct cell cycle abnormalities by promoting DNA repair. The DNA-binding domain of the p53 protein itself has endonuclease activity and can directly participate in the excision of mismatched nucleotides. Simultaneously, p53 can bind to and regulate the activity of nucleotide excision repair factors XPB and XPD, affecting their DNA recombination and repair functions. Furthermore, p53 can form a complex with p21 and GADD45, utilizing its own 3'-5' exonuclease activity to play a role in DNA repair. This allows cells to enter the S phase after completing DNA repair, ensuring the accuracy of DNA replication [6].

5. Synergistic Effects of p53-related Signaling Pathways in G1/S Transition Correction

The precise regulation of the cell cycle is a complex and delicate process. In the correction mechanism of the G1/S transition, multiple signaling pathways intertwine and synergize. This chapter will delve into the synergistic relationship between p53 and other key signaling pathways, including the ATM/ATR signaling pathway, Rb-E2F signaling pathway, and miRNA regulatory network. We will analyze how they interact and restrict each other, forming a tight regulatory network to ensure that cells maintain a normal physiological state during the G1/S transition and prevent cell cycle dysregulation from causing diseases.

5.1 p53 and ATM/ATR Signaling Pathway

The ATM/ATR signaling pathway plays an indispensable role in the cellular response to DNA damage and is a key component of the intracellular DNA damage response mechanism. When cells suffer DNA damage caused by factors such as UV light, ionizing radiation, or chemical substances, the ATM/ATR signaling pathway is rapidly activated. ATM/ATR kinases then phosphorylate the p53 protein, transitioning it from an inactive to an active state and involving it in the regulation of the cell cycle [7]. It's worth noting that p53 is not just a passive recipient of regulation; it can also regulate the activity of the ATM/ATR signaling pathway, forming a positive feedback loop. This loop enhances the cell's responsiveness to DNA damage and significantly boosts its repair capability, providing a solid guarantee for maintaining DNA integrity during the critical G1/S transition phase. This significantly reduces the risk of cell carcinogenesis or death due to unrepaired DNA damage.

5.2 p53 and Rb-E2F Signaling Pathway

The Rb-E2F signaling pathway plays a pivotal role in the transition of cells from G1 to S phase and is a key member of the core regulatory pathway. Through specific molecular mechanisms, p53 can transcriptionally activate

the p21 gene. The generated p21 protein effectively inhibits the phosphorylation of Rb protein by the cyclin-CDK complex. This allows Rb to continuously bind to the transcription factor E2F, successfully impeding E2F's transcriptional activity and ultimately achieving precise regulation of the Rb-E2F signaling pathway [8]. Conversely, abnormalities in the Rb-E2F signaling pathway can interfere with p53's activity and function. These two components are closely linked and coordinated, working together to ensure the orderly and normal progression of the cell's G1/S transition. This collaboration is crucial for maintaining the stability and accuracy of the cell cycle process, as well as the normal growth, proliferation, and genomic integrity of cells.

5.3 p53 and miRNA Regulatory Network

p53 exhibits diverse and delicate mechanisms in regulating the cell cycle process, where regulating miRNA expression to influence the cell cycle is a crucial aspect. p53 can precisely transcriptionally activate miRNAs like miR-34a, which promote the normalization of the cell cycle, or inhibit the expression of miRNAs that may interfere with normal processes, such as miR-145. These regulated miRNAs act on key genes like cell cycle proteins, CDKs, and E2Fs, indirectly and effectively regulating the G1/S transition [9]. Simultaneously, some miRNAs also have the ability to regulate p53 expression and activity in reverse, forming a complex miRNA-p53 regulatory network. When the cell cycle is abnormal, they work together to exert a corrective effect, maintaining stable cell cycle operation and ensuring normal physiological cell functions [10].

6. Conclusion

The tumor suppressor gene p53 plays a crucial role in maintaining the normal progression of the cell cycle and preventing cell carcinogenesis through precise monitoring and various correction mechanisms during the G1/S transition. It can not only transcriptionally activate the p21 gene to inhibit the activity of the cell cycle protein-CDK complex, causing cell cycle arrest in the G1 phase, but also induce apoptosis or promote DNA repair to eliminate or correct abnormal cells. Additionally, the synergistic effects between p53 and other signaling pathways further enhance its ability to correct abnormalities during the G1/S transition. Delving into the correction mechanisms of p53 for abnormalities during the G1/S transition has important theoretical and practical significance in revealing the molecular mechanisms of tumor development, developing novel tumor treatment strategies, and preventing and treating cancer. However, there are still many unknowns about p53's role in cell cycle regulation, requiring further in-depth research to more comprehensively understand its complex biological functions and regulatory mechanisms.

Disclosure statement

The author declares no conflict of interest.

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