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Mini-Review

Cyclin B: Structure, Function, Role in Diseases and Therapeutic Approaches

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Abstract:

Cyclin B is a key regulatory protein in the cell cycle, predominantly governing the transition from the G2 phase to mitosis (M phase). By associating with cyclin-dependent kinase 1 (CDK1), it forms the active Cyclin B-CDK1 complex, which triggers a cascade of phosphorylation events essential for mitotic entry and progression. Dysregulation of Cyclin B expression and activity has been extensively linked to various pathological conditions, especially cancers, facilitating abnormal cell division and tumor development. This review systematically summarizes the structural characteristics, biological functions, roles in disease pathogenesis, and current therapeutic strategies related to Cyclin B. In-depth understanding of Cyclin B's mechanisms can provide a robust basis for the development of more effective and targeted therapeutic interventions.

Keywords: cyclin B; cell cycle; mitosis; cancer; targeted therapy; disease

1. Introduction:

The cell cycle is a precisely regulated process that ensures the accurate replication and division of cells, maintaining tissue homeostasis and organismal development. Cyclin B, as a critical member of the cyclin family, plays a pivotal role in the transition from the G2 phase to the M phase, a period marked by chromosome segregation and cell division. Upon binding to CDK1, Cyclin B activates the kinase, and the resulting Cyclin B-CDK1 complex phosphorylates a plethora of substrates, orchestrating the morphological and physiological changes necessary for mitosis. In normal cells, the expression, localization, and activity of Cyclin B are tightly controlled by multiple regulatory mechanisms. However, in pathological states, particularly in cancers, disruptions in Cyclin B regulation lead to uncontrolled cell division, contributing significantly to disease progression. Exploring the functions, mechanisms, and therapeutic implications of Cyclin B is crucial for understanding disease mechanisms and devising innovative treatment strategies.

2. Structure of Cyclin B

2.1 Domain structure

Cyclin B proteins feature a conserved structural framework. They possess a characteristic cyclin box, approximately 100 amino acids in length, which is responsible for binding to CDK1. The cyclin box folds into an α-helical structure that fits precisely into the corresponding binding groove on CDK1, enabling the formation of the Cyclin B-CDK1 complex. Besides the cyclin box, Cyclin B has an N-terminal region and a C-terminal region. The N-terminal region often contains regulatory motifs, such as the destruction box (also known as the D-box), which is a short amino acid sequence (RXXL, where R is arginine, X is any amino acid, and L is leucine). The D-box is recognized by the anaphase-promoting complex/cyclosome (APC/C), a ubiquitin ligase complex that marks Cyclin B for degradation during mitotic exit. The C-terminal region of Cyclin B may participate in protein-protein interactions, influencing the subcellular localization and functional regulation of the Cyclin B-CDK1 complex [1].

2.2 Structural insights from crystallography

X-ray crystallography and cryo-electron microscopy have provided detailed structural information about the Cyclin B-CDK1 complex. These studies have revealed the precise molecular interactions during complex formation, showing how Cyclin B binding induces conformational changes in CDK1, exposing the active site and enhancing its kinase activity. The structural details also elucidate the interactions between the Cyclin B-CDK1 complex and its substrates, which is fundamental for the rational design of small molecule inhibitors targeting this complex [2].

3. Biological functions of Cyclin B

3.1 Regulation of the cell cycle

The primary function of Cyclin B is to drive cells from the G2 phase into mitosis. As cells progress through the G2 phase, the levels of Cyclin B gradually increase. Once sufficient Cyclin B accumulates and binds to CDK1, the activated Cyclin B-CDK1 complex phosphorylates numerous key substrates. These include proteins involved in chromatin

condensation, such as histone H1, which causes the chromatin to compact and become visible as chromosomes. The complex also phosphorylates components of the nuclear lamina, leading to the breakdown of the nuclear envelope, and proteins related to spindle apparatus formation, ensuring proper chromosome segregation. Additionally, Cyclin B-CDK1 activity is tightly regulated by feedback mechanisms. For example, it phosphorylates and activates the APC/C, which then targets Cyclin B for degradation, triggering the exit from mitosis and the transition to the next cell cycle phase [3].

3.2 Non-cell cycle functions

Although Cyclin B is best known for its role in cell cycle regulation, emerging evidence suggests it may have non-cell cycle functions. In some cell types, Cyclin B has been implicated in the regulation of gene transcription. It can interact with transcription factors and modulate their activity, influencing the expression of genes involved in various cellular processes. Moreover, Cyclin B may play a role in the response to cellular stress. Under certain stress conditions, such as DNA damage, the regulation of Cyclin B can be altered, and its function may extend beyond cell cycle control to participate in cellular survival or death decisions [4].

4. Cyclin B in diseases

4.1 Cancers

Dysregulation of Cyclin B is commonly observed in many types of cancers. Overexpression of Cyclin B1, the most well-studied member of the Cyclin B family, is frequently detected in breast cancer, colorectal cancer, and lung cancer. In cancer cells, abnormal accumulation of Cyclin B1 can lead to premature entry into mitosis, resulting in chromosomal instability due to incomplete DNA replication or repair. This genomic instability promotes tumorigenesis and cancer progression. Additionally, high levels of Cyclin B1 are associated with poor prognosis in several cancers, as it can confer resistance to chemotherapy and radiotherapy by interfering with the normal cell cycle checkpoint responses. For instance, in some cancer cells, overactive Cyclin B-CDK1 may bypass the G2/M DNA damage checkpoint, allowing damaged cells to divide and potentially giving rise to more aggressive tumor subtypes [5].

4.2 Other diseases

Cyclin B is also involved in non-cancerous diseases. In neurodegenerative diseases, such as Huntington's disease, dysregulation of Cyclin B has been reported. Aberrant activation of the Cyclin B-CDK1 pathway in neurons may disrupt normal neuronal functions, leading to neuronal apoptosis and contributing to the progressive neurodegeneration. In cardiovascular diseases, abnormal regulation of Cyclin B can affect the proliferation and differentiation of cardiac myocytes and vascular smooth muscle cells. Dysregulation of Cyclin B may contribute to the development of cardiac hypertrophy and vascular remodeling, which are important pathological processes in heart failure and atherosclerosis, respectively [6].

5. Therapeutic strategies targeting Cyclin B

5.1 Small molecule inhibitors

Small molecule inhibitors targeting the Cyclin B-CDK1 axis have been a focus of drug development. Some inhibitors are designed to bind to the ATP-binding pocket of CDK1, preventing the phosphorylation of downstream substrates and blocking the entry into mitosis. For example, RO-3306 is a highly selective inhibitor of CDK1 that specifically targets the Cyclin B-CDK1 complex. It has shown potential in preclinical studies by inducing cell cycle arrest at the G2/M phase in cancer cells. However, like many kinase inhibitors, challenges such as off-target effects and the development of resistance limit its clinical application. Currently, efforts are being made to develop more selective and potent small molecule inhibitors that can specifically target the abnormal activity of the Cyclin B-CDK1 complex in disease cells while minimizing toxicity to normal cells [7].

5.2 Antibody-based therapies

Antibody-based approaches targeting Cyclin B are emerging as promising therapeutic strategies. Monoclonal antibodies can be engineered to specifically bind to Cyclin B, either blocking its interaction with CDK1 or promoting its degradation. These antibodies can also be conjugated with cytotoxic payloads to directly eliminate cells with dysregulated Cyclin B expression. Although still in the preclinical and early clinical stages, antibody-based therapies offer the advantage of high specificity, enabling more targeted treatment compared to small molecule inhibitors [8].

5.3 Combination therapies

Combination therapies that combine Cyclin B-CDK1 inhibitors with other anti-cancer agents or treatment modalities are being actively explored. For example, combining CDK1 inhibitors with DNA-damaging chemotherapy drugs may enhance the sensitivity of cancer cells to treatment by further disrupting the cell cycle and preventing the repair of damaged DNA. Additionally, combining Cyclin B-targeted therapies with immunotherapies may modulate the tumor microenvironment and enhance anti-tumor immune responses. In non-cancer diseases, combination therapies involving Cyclin B regulation along with other disease-specific treatments may also provide more effective therapeutic options [9].

6. Challenges and future directions

Despite the progress in Cyclin B-targeted therapy, several challenges remain. One major challenge is the development of resistance to inhibitors in cancer cells. Resistance mechanisms may include mutations in CDK1 or Cyclin B that prevent inhibitor binding, upregulation of alternative kinases that can compensate for the inhibited Cyclin B-CDK1 activity, or alterations in the regulatory pathways that control Cyclin B expression and degradation. Understanding these resistance mechanisms and developing strategies to overcome them are crucial for improving treatment efficacy. Another challenge is the potential off-target effects of small molecule inhibitors, which may affect normal cells with high proliferative rates, such as those in the bone marrow, gut epithelium, and hair follicles. Developing more selective and less toxic inhibitors, as well as optimizing treatment regimens, is an important goal. In the future, further research on the non-cell cycle functions of Cyclin B may uncover new therapeutic targets and strategies. The integration of advanced technologies, such as artificial intelligence in drug design, single-cell sequencing to understand cellular heterogeneity, and gene editing tools to study the function of Cyclin B in disease models, may accelerate the discovery of novel Cyclin B-targeted drugs and combination therapies.

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