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Research Progress on the CDK4/6 Signaling Pathway and Clinical Application of Its Inhibitors in HR+/HER2- Breast Cancer

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ABSTRACT

Breast cancer is a common malignant tumor among women worldwide, with the HR+/HER2- subtype (Luminal type) accounting for 60%-70% of all cases. Endocrine therapy has long been the standard treatment for this subtype; however, 30% of patients exhibit primary resistance, and most initial responders develop acquired resistance after treatment, resulting in a significant disease burden. Dysregulation of the cell cycle is a key mechanism underlying endocrine resistance in this subtype. Cyclin-dependent kinases 4/6 (CDK4/6) form a complex with cyclin D, which phosphorylates the retinoblastoma protein (Rb) to relieve its inhibitory effect on E2F transcription factors, thereby promoting G1–S transition. Aberrant activation of this pathway (e.g., cyclin D1 overexpression, CDK6 amplification) is directly associated with endocrine resistance, making CDK4/6 a critical therapeutic target.

Since 2015, CDK4/6 inhibitors represented by palbociclib have been developed. These inhibitors selectively suppress CDK4/6 activity to block Rb phosphorylation, arresting tumor cell cycles at the G0/G1 phase. Clinical studies have confirmed that combining CDK4/6 inhibitors with endocrine therapy (aromatase inhibitors [AIs] or selective estrogen receptor degraders [SERDs]) extends the median progression-free survival (mPFS) of patients with advanced HR+/HER2- breast cancer from 9-14 months (with conventional endocrine therapy alone) to 24-30 months, reducing the risk of disease progression by 40%-50%. This combination regimen has been designated as a Category I recommendation for first-line treatment of advanced HR+/HER2- breast cancer in guidelines issued by authoritative organizations such as the NCCN(2024) [16], ESMO(2024) [17], and CSCO(2024) [18].

Nevertheless, the clinical application of CDK4/6 inhibitors faces new challenges: approximately 30% of patients have primary resistance, and most initially sensitive patients develop secondary resistance 12-36 months after treatment initiation. The mechanisms of resistance are complex, involving Rb loss-of-function, PI3K/AKT pathway activation, and ESR1 mutations, among others. Clinically, there is a lack of reliable predictive biomarkers and standardized post-resistance intervention strategies. This article systematically reviews the characteristics of HR+/HER2- breast cancer, the regulatory mechanism of the CDK4/6 signaling pathway, the clinical value of CDK4/6 inhibitors, and the issue of drug resistance, aiming to provide a theoretical basis for optimizing clinical treatment decisions and overcoming resistance.

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1. Global and Chinese Epidemiological Status of Breast Cancer

Breast cancer is the most common malignant tumor in women globally and a leading cause of cancer-related deaths in females, posing a major public health challenge. Statistics show that it accounts for 31% of new female cancer cases and 15% of cancer-related deaths worldwide [1]. In China, although the incidence rate (36.1 per 100,000) and mortality rate (8.8 per 100,000) of female breast cancer are relatively low globally, both have shown a continuous upward trend, with annual percentage changes of 3.9% and 1.1%, respectively. Due to China's large population base, the number of new cases and deaths of female breast cancer in the country ranks first in the world, accounting for 17.6% and 15.6% of the global totals, respectively, leading to an increasingly heavy disease burden [3,7].

From the perspective of molecular subtypes, breast cancer can be classified into multiple categories based on the expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2). Among these, the luminal type (i.e., HR+/HER2- subtype) is the most common, accounting for approximately 60%-70% of all breast cancer cases [2,4]. The development and progression of this subtype are closely associated with abnormal hormone signaling pathways; therefore, endocrine therapy has long been the standard treatment strategy. Key endocrine therapeutic agents include selective estrogen receptor modulators (SERMs, such as tamoxifen, suitable for pre- and postmenopausal patients), aromatase inhibitors (AIs, such as letrozole, used in postmenopausal patients), and selective estrogen receptor degraders (SERDs, such as fulvestrant, indicated for postmenopausal patients with drug resistance) [5]. However, the clinical benefits of endocrine therapy are limited by drug resistance: approximately 30% of patients have primary resistance, and almost all initial responders develop acquired resistance after treatment, eventually leading to disease recurrence or progression [6-7]. Thus, more effective therapeutic strategies are urgently needed to address this dilemma.

In-depth studies have revealed that dysregulation of the cell cycle is one of the key mechanisms underlying endocrine resistance in HR+/HER2- breast cancer. Cyclin-dependent kinases 4/6 (CDK4/6) form a complex with cyclin D, which phosphorylates the retinoblastoma protein (Rb) to relieve its inhibitory effect on E2F transcription factors, thereby promoting G1–S transition Aberrant activation of this pathway (e.g., cyclin D1 overexpression, CDK6 amplification) is directly associated with endocrine resistance, and inactivation of Rb via phosphorylation also predicts poor efficacy of endocrine therapy [8]. Therefore, CDK4/6 has become a critical therapeutic target for HR+/HER2- breast cancer.

Since 2015, CDK4/6 inhibitors represented by palbociclib have been successively developed. These inhibitors selectively suppress CDK4/6 activity to block Rb phosphorylation, arresting tumor cell cycles at the G0/G1 phase and significantly revolutionizing the treatment landscape of HR+/HER2- breast cancer. Clinical studies have confirmed that combining CDK4/6 inhibitors with endocrine therapy (AIs or SERDs) extends the median progression-free survival (mPFS) of patients with advanced disease from 9-14 months (with conventional endocrine therapy alone) to 24-30 months, reducing the risk of disease progression by 40%-50% [9]. This combination regimen has been designated as a Category I recommendation for first-line treatment of advanced HR+/HER2- breast cancer in guidelines issued by authoritative organizations such as the NCCN(2024) [16], ESMO(2024) [17], and CSCO(2024) [18].

However, with the widespread application of CDK4/6 inhibitors, new challenges have emerged: approximately 30% of patients have primary resistance, and most initially sensitive patients develop secondary resistance 12-36 months after treatment initiation [7]. Moreover, the mechanisms of resistance are complex (e.g., Rb loss-of-function, PI3K/AKT pathway activation, ESR1 mutations), and there is a lack of reliable predictive biomarkers and standardized post-resistance intervention strategies in clinical practice [10-11]. Against this backdrop, systematically reviewing the characteristics of HR+/HER2- breast cancer, the clinical value of CDK4/6 inhibitors, and the issue of drug resistance is of great significance for optimizing clinical decision-making.

2. Targeted Mechanism of the CDK4/6 Signaling Pathway

2.1. Overview of the Cell Cycle

Since the 1990s, studies on the cell cycle using yeast as a model have been carried out successively, and scientists have deciphered the mitotic process of eukaryotic cells. The cell cycle refers to the entire process from the completion of one cell division to the end of the next division. As a fundamental process of cell life activities, it regulates the transition of cells from a quiescent state to a growth and proliferation state.

The cell cycle consists of distinct phases, including the G1 phase (Gap 1 phase, pre-DNA synthesis phase), S phase (synthesis phase, DNA replication phase), G2 phase (Gap 2 phase, pre-mitotic phase), and M phase (mitotic phase). As shown in Fig. 1, the G1 phase has the longest duration, followed by the S phase, G2 phase, and M phase (the shortest). The M phase can be further divided into four stages: prophase, metaphase, anaphase, and cytokinesis. Most cells in the adult human body are in the G1 phase or the quiescent G0 phase.

There are two "decision checkpoints" in the G1 and G2 phases, at which cells determine whether to proceed to the next phase based on the current environmental conditions (e.g., G1–S transition, or from the G2 phase to the M phase). The "decision checkpoint" in the G1 phase is also known as the restriction point (R point). Before the R point, the proliferative state of cells is regulated by extracellular signals, such as growth factors and Wnt signals. If cells suffer DNA damage due to external factors (e.g., radiation, stress), they will initiate DNA repair programs and not pass the R point. After the R point, cells are no longer affected by extracellular signals; instead, they proceed through the G1 phase under the control of an autonomous program, synthesize DNA and tubulin, and ultimately complete cell division to form two daughter cells [12].

The cell cycle is divided into G0 (quiescent phase), G1, S, G2, and M phases. The R point in the G1 phase serves as the boundary between extracellular signal-dependent and cell-autonomous program-controlled stages. Before the R point, cell proliferation relies on

extracellular signals (e.g., growth factors); after passing the R point, cells proceed through G1–S transition and subsequent phases independently [12].

2.2. Regulatory Mechanism of the Cell Cycle

The progression of the cell cycle is a complex regulatory process, primarily driven by a core cell cycle mechanism located in the cell nucleus. This mechanism consists of cyclins and their catalytic partners—cyclin-dependent kinases (CDKs).

Cyclins are a class of proteins that are periodically synthesized and degraded during cell cycle regulation. They were first discovered by Tom Evans' team in 1983 during studies on the sea urchin cell cycle. The expression of cyclins is selectively activated or inhibited at different stages of the cell cycle, thereby promoting or arresting the progression of specific cell cycle phases. The name "cyclin" is derived from this periodic expression pattern.

CDKs are a family of serine/threonine kinases that require binding to cyclins to exert their biological functions. They regulate the cell cycle mainly by phosphorylating serine or threonine residues of target proteins; this phosphorylation can either activate or inhibit specific proteins, thereby affecting cell cycle progression. Cyclins and CDKs are closely associated—CDKs only exhibit activity when bound to specific cyclins.

In vertebrates, cyclins are classified into types A, B, D, E, F, G, H, etc., and can bind to corresponding CDKs at specific stages to form cyclin-CDK complexes (e.g., cyclin D-CDK4/6, cyclin E-CDK2, cyclin A-CDK2, cyclin H-CDK7, cyclin A-CDK1, and cyclin B-CDK1). As shown in Fig. 2, different cyclin-CDK complexes are activated at specific stages of the cell cycle and phosphorylate their target proteins. Each group of cyclin-CDK complexes can regulate the orderly progression of each cell cycle phase by triggering the expression of the next group of cyclin-CDK complexes and other related cyclins [8,13].

Cyclin-CDK complexes (e.g., cyclin D-CDK4/6, cyclin E-CDK2) are sequentially activated at different cell cycle phases. Cyclin D-CDK4/6 initiates G1 phase progression by phosphorylating Rb; cyclin E-CDK2 promotes G1–S transition; cyclin A-CDK2 and cyclin A-CDK1 regulate S phase and G2 phase progression, respectively; cyclin B-CDK1 drives M phase execution. Inhibitory factors (e.g., INK4 family, KIP/CIP family) and checkpoint proteins (e.g., WEE1, CDC25) synergistically maintain the balance of cell cycle progression [13].

In normal cells, the expression and activity of cyclins and CDKs are strictly regulated in a spatial and temporal manner to ensure the smooth progression of the cell cycle. In cancer cells, however, overexpression or inactivation of cyclins or CDKs may lead to cell cycle dysregulation, allowing cells to proliferate continuously even in the absence of extracellular signals or under harsh environmental conditions.

2.3. Role of CDK4/6 in the Cell Cycle

To date, 20 distinct CDKs have been identified in the human body. Most members of the CDK family have a protein length of less than 500 amino acids (aa), and the kinase domain— which exerts the core function—accounts for most of the amino acid sequence. Based on their functions, CDKs can be classified into three categories [14]:

1. Cell cycle regulators: CDK1, 2, 3, 4, and 6;
2. Transcription regulators: CDK7, 8, 9, 12, 13, and 19;
3. Regulators with diverse or undefined functions: CDK5, 10, 11, 14, 15, 16, 17, 18, and 20.

Amino acid sequence analysis reveals that CDK4 and CDK6 share 71% homology and have similar functions, making them highly homologous cell cycle kinases. CDK4/6 and D-type cyclins (cyclin D1/D2/D3) are core molecules that drive the initiation of the entire cell cycle. Extracellular growth factor signals stimulate the activation of the cyclin D-CDK4/6 complex via the mitogen-activated protein kinase (MAPK) signaling pathway to initiate the cell cycle [15].

During cell division, the activated cyclin D-CDK4/6 complex phosphorylates the substrate retinoblastoma protein (Rb), promoting the dissociation of Rb from E2F1/2/3. This dissociation activates the transcriptional function of E2F1/2/3, which then cooperates with DP1/2 to promote the translation of cyclin E and enzymes/proteins required for the S phase, thereby enabling the smooth G1–S transition. In contrast, unphosphorylated Rb can bind tightly to the transcription factors E2F1/2/3, inhibiting their transcriptional activity and ultimately inducing cell cycle arrest at the G1 phase. The specific mechanism is shown in Fig. 3.

Notably, the phosphorylation of Rb by the activated cyclin D-CDK4/6 complex is the core molecular mechanism regulating the G1-S transition of the cell cycle [8].

Mitogens activate the cyclin D-CDK4/6 complex, which phosphorylates hypophosphorylated Rb. Phosphorylated Rb (pRb) dissociates from the E2F-DP complex, releasing E2F1/2/3 to transcriptionally activate genes related to G1–S transition (e.g., cyclin E). Unphosphorylated Rb remains bound to E2F, inhibiting G1–S transition and arresting cells in the G1 phase [12].

2.4. Mechanism of Action of CDK4/6 Inhibitors

CDKs exhibit functional specificity in cell cycle regulation: the occurrence and proliferation of certain tumors are highly dependent on the abnormal activity of specific CDKs, while normal tissues can maintain physiological functions through functional compensation among different CDKs. This "tumor dependence-normal compensation" difference makes CDKs important potential targets for precision cancer therapy.

As key binding partners of cyclin D, CDK4/6 exhibit abnormally activated activity in various tumors. Enhanced CDK4/6 activity drives the G1–S transition of the cell cycle and can continuously promote cell division even in the absence of growth factor signals, thus becoming one of the core drivers of uncontrolled proliferation of cancer cells.

In the regulation of the normal cell cycle, two core families of cyclin-dependent kinase inhibitors (CKIs) maintain cycle homeostasis:

1. The INK4 (inhibitors of kinase 4) family, including p16INK4A, p15INK4B, p18INK4C, and p19INK4D. Among these, p16INK4A has high affinity for CDK4/6 and can form a complex by directly binding to CDK4/6, competitively blocking their interaction with cyclin D;
2. The CIP/KIP (CDK interaction protein/kinase inhibitor protein) family, including p21CIP1, p27KIP1, and p57KIP2. These proteins inhibit CDK activity through multiple mechanisms.

These two families of CKIs work together to prevent the phosphorylation of Rb, achieving precise regulation of cell cycle progression [8,11].

In cancer cells, the cyclin D-CDK4/6-p16INK4A-Rb pathway often exhibits significant abnormalities: on the one hand, genes encoding D-type cyclins (CCND1, CCND2, CCND3), CDK4, or CDK6 frequently undergo amplification or rearrangement, leading to a significant increase in the expression levels of the corresponding proteins; on the other hand, negative regulators of CDK4/6 (e.g., p16INK4A) are often inactivated due to gene mutations, methylation, or other mechanisms. These changes collectively lead to the overactivation of cyclin D-CDK4/6 kinases, inactivating the Rb-mediated cell cycle inhibitory function and ultimately allowing cancer cells to escape the regulation of extracellular mitogenic and anti-mitogenic signals, entering a state of uncontrolled proliferation [8,11].

Based on the aforementioned pathway abnormalities, the mechanism of action of CDK4/6 inhibitors can be summarized as follows: by specifically binding to the active pocket of CDK4/6 and inhibiting their kinase activity, CDK4/6 inhibitors reduce the phosphorylation level of Rb protein, arrest the tumor cell cycle at the G0/G1 phase, and ultimately block the proliferation of tumor cells, thereby achieving an anti-tumor effect.

3. Conclusions and Future Perspectives

This study systematically analyzed the core role of the CDK4/6 signaling pathway in cell cycle regulation and its targeted mechanism, clarifying the molecular regulatory logic of this pathway and the scientific basis for targeted intervention. The main conclusions are as follows:

First, the orderly progression of the cell cycle depends on multi-stage regulation and "decision checkpoint" control. The eukaryotic cell cycle is divided into the G1, S, G2, and M phases, with significant differences in the duration of each phase. The G1 phase is the longest, while the M phase is the shortest and can be further divided into prophase, metaphase, anaphase, and cytokinesis. Most cells in the adult human body are in the G1 phase or the quiescent G0 phase. There are two "decision checkpoints" in the cell cycle (at the G1 and G2 phases). Before the R point (in the G1 phase), cell proliferation depends on extracellular signals such as growth factors; if DNA damage occurs, cells initiate repair programs and arrest at the G1 phase. After the R point, cells enter an autonomous program-controlled stage to ensure the stable progression of the division process. This provides a foundation for subsequent analysis of the phase-specific role of CDK4/6.

Second, the core mechanism of cell cycle regulation lies in the specific activation and functional synergy of cyclin-CDK complexes. Cyclins are periodically synthesized and degraded; first discovered in sea urchin cells in 1983, they are selectively activated at different stages of the cell cycle to promote or arrest progression. CDKs require binding to specific cyclins to exhibit serine/threonine kinase activity and regulate cell cycle progression by phosphorylating target proteins. In vertebrates, cyclins are classified into types A, B, D, E, etc., and can form complexes with corresponding CDKs (e.g., cyclin D-CDK4/6, cyclin E-CDK2). Each group of cyclin-CDK complexes enables the orderly connection of cell cycle phases by triggering the expression of the next group of molecules. In normal cells, the spatiotemporal expression of cyclins and CDKs is strictly controlled; in cancer cells, however, their abnormal expression or inactivation leads to cell cycle dysregulation, creating conditions for tumor proliferation.

Third, CDK4/6 are key molecules driving the G1-S transition of the cell cycle. Among the 20 CDKs identified in humans, CDK4/6 belong to the cell cycle regulator category. They share 71% amino acid sequence homology, have similar functions, and require binding to D-type cyclins (cyclin D1/D2/D3) to form active complexes. Extracellular growth factor signals can activate this complex via the MAPK pathway. The activated cyclin D-CDK4/6 complex phosphorylates Rb, promoting its dissociation from E2F1/2/3 and activating the transcriptional function of E2F. This then cooperates with DP1/2 to promote the translation of cyclin E and enzymes/proteins required for the S phase, ultimately enabling the G1-S transition. In contrast, unphosphorylated Rb binds tightly to E2F to inhibit its activity, arresting cells at the G1 phase. These findings confirm that Rb phosphorylation by cyclin D-CDK4/6 is the core regulatory mechanism of the G1-S transition.

Fourth, the targeted mechanism of CDK4/6 inhibitors is based on pathway abnormalities and the "tumor dependence-normal compensation" difference. In normal cells, the INK4 family (e.g., p16INK4A) blocks the interaction between CDK4/6 and cyclin D by competitive binding, while the CIP/KIP family (e.g., p21CIP1) inhibits CDK activity through multiple mechanisms. These two families of CKIs work together to prevent Rb phosphorylation and maintain cycle homeostasis. In cancer cells, however, gene amplification/rearrangement of cyclin D or CDK4/6, as well as inactivation of negative regulators such as p16INK4A, lead to the overactivation of cyclin D-CDK4/6 and the loss of Rb inhibitory function, allowing cells to proliferate continuously independent of external signals. Based on this, CDK4/6 inhibitors can specifically bind to the active pocket of CDK4/6, inhibit their kinase activity, reduce Rb phosphorylation, arrest tumor cell cycles at the G0/G1 phase, and ultimately block proliferation—providing a clear pathway for targeted therapy.

In summary, the CDK4/6 signaling pathway forms a core regulatory network for the G1-S transition of the cell cycle through a molecular cascade involving cyclin D binding, Rb phosphorylation, and E2F activation. Aberrant activation of this pathway in tumors provides a target for targeted intervention, and CDK4/6 inhibitors—by precisely inhibiting kinase activity and restoring cell cycle arrest—

have become a critical tool for cancer therapy. The clarification of their mechanism of action also provides a theoretical basis for the subsequent optimization of targeted strategies.

Despite the remarkable clinical achievements of CDK4/6 inhibitors, the challenge of drug resistance and the lack of predictive biomarkers remain major bottlenecks limiting their long-term efficacy. Future research should focus on several directions: first, exploring multi-omics-based predictive biomarkers (e.g., combined genomic, transcriptomic, and proteomic signatures) to identify patients most likely to benefit from CDK4/6 inhibitor therapy and stratify high-risk populations for resistance. Second, deciphering the crosstalk between the CDK4/6 pathway and other oncogenic pathways (e.g., PI3K/AKT, MAPK, and mTOR) to develop rational combination therapies that overcome adaptive resistance—for example, combining CDK4/6 inhibitors with PI3K inhibitors or immunotherapies to enhance anti-tumor synergy. Third, optimizing the application of CDK4/6 inhibitors in early breast cancer, including exploring appropriate adjuvant/neoadjuvant therapy regimens and defining patient populations that may benefit from extended treatment durations. Fourth, developing next-generation CDK4/6 inhibitors with higher selectivity, better tissue penetration, or the ability to overcome specific resistance mechanisms (e.g., Rb loss or ESR1 mutations). Additionally, exploring the role of CDK4/6 inhibitors in other cancer types with dysregulated CDK4/6 signaling (e.g., melanoma, lung cancer, and ovarian cancer) may expand their therapeutic spectrum. Finally, real-world studies and long-term follow-up data are needed to validate the efficacy and safety of CDK4/6 inhibitor-based regimens in diverse clinical settings, guiding the refinement of clinical guidelines and personalized treatment strategies.

Author Contribution

Xiaowen Li contributed to the conception and design of the study, drafted the initial manuscript, and conducted the literature review on the CDK4/6 signaling pathway and clinical trials of its inhibitors.

Jinfeng He was responsible for data curation, validation of clinical guidelines, and assisted in the writing and critical revision of the manuscript.

Chengwen Song supervised the overall project, reviewed the final manuscript for intellectual content and accuracy, and is the corresponding author responsible for submission and correspondence.

All authors have read and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

Compliance with Ethical Standards

This article is a narrative review based on previously published literature and does not involve any new studies with human participants or animals performed by any of the authors. Therefore, ethical approval and informed consent were not required.

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Competing Interest declaration

The author declare that, to their knowledge, they have no financial, personal, or professional relationships that could be construed as a potential competing interest regarding the work described in this manuscript.

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Appendices

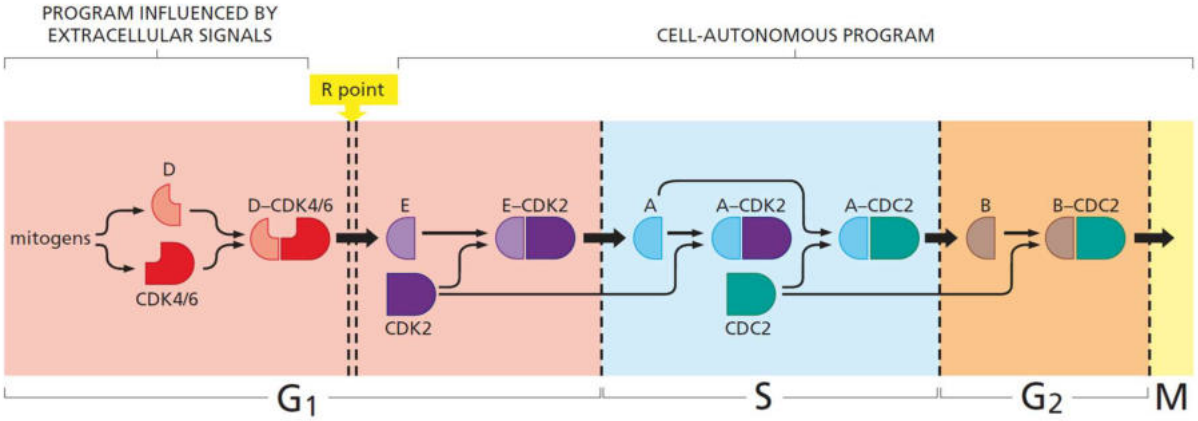


Fig. 1. Stage Division of Cell Division Cycle Regulation: Extracellular Signal-Dependent Phase and Cell Autonomous Program-Controlled Phase Bounded by the R Point.

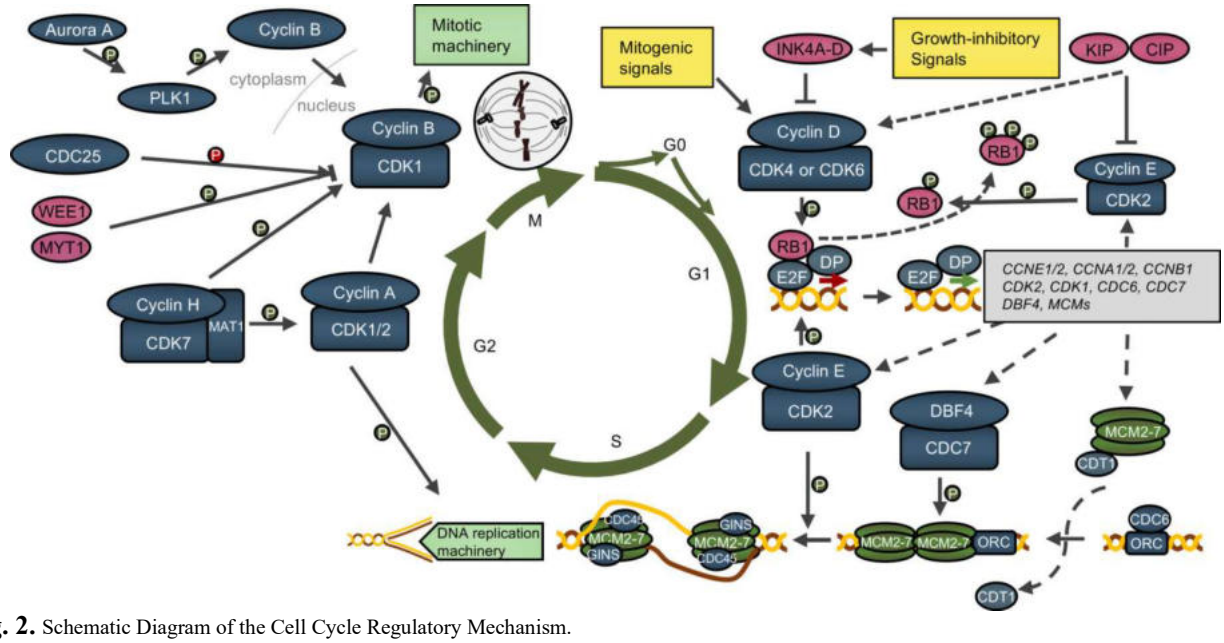


Fig. 2. Schematic Diagram of the Cell Cycle Regulatory Mechanism.

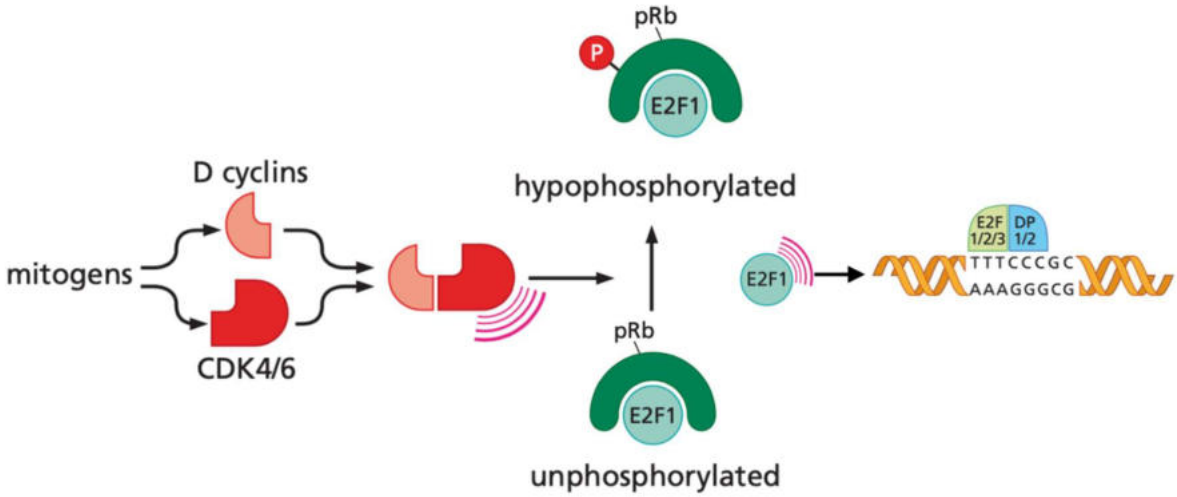


Fig. 3. Schematic Diagram of Cell Cycle Regulation by Cyclin D-CDK4/6 via Rb Phosphorylation