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RB1 in Cancer: A Key Driver of Multisystem Carcinogenesis

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Abstract: The RB1 gene is a tumor suppressor whose primary function is to regulate the cell cycle through the retinoblastoma protein (pRB). RB1 mutations are the primary cause of retinoblastoma. Beyond retinoblastoma, RB1 inactivation is associated with many other human cancers, including glioblastoma, multiple myeloma, osteosarcoma, melanoma, small cell lung cancer, bladder, prostate, breast, and endometrial cancers. Mutations in RB1 disrupt the G1 to S phase checkpoint, promoting uncontrolled cell proliferation and genomic instability. Advanced studies highlight the role of RB1 in immune evasion and resistance to therapy, particularly in prostate and breast cancers. RB1 gene loss in small cell lung cancer and triple-negative breast cancer represents a key molecular feature that influences treatment resistance and prognosis. RB1 status serves as a predictive biomarker in clinical oncology and guides the development of targeted therapies, especially cyclin-dependent kinase 4/6 inhibitors. Understanding RB1 is crucial for advancing personalized cancer treatment and improving patient outcomes across different malignancies.

Keywords: *RB1 Gene; Cell Cycle; Carcinogenesis; Tumor Suppressor; Retinoblastoma.*

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I. INTRODUCTION

Cancer encompasses a diverse group of diseases characterized by uncontrolled cell growth, resistance to cell death, and the ability to invade and spread. Cancer develops through tumorigenesis, a complex biological process driven by the gradual buildup of genetic and epigenetic changes. These changes disrupt essential regulatory pathways that control the cell cycle, DNA repair, apoptosis, and cell differentiation. Tumor suppressor genes play a vital role in preventing cancer. They help limit excessive cell division, maintain genomic stability, and support orderly transitions in the cell cycle [1,2]. When these genes are mutated, deleted, or silenced, critical growth control systems fail. This failure promotes cancer progression and tumor development. One of the most studied tumor suppressor genes is RB1 (Retinoblastoma 1), situated on chromosome 13q14. RB1 was the first tumor suppressor gene to be discovered, and its identification greatly enhanced our understanding of cancer biology. This gene produces the retinoblastoma protein (pRB), a key regulator of the cell cycle [3,4]. By controlling the G1/S checkpoint, RB1 integrates external growth signals with internal regulatory pathways to determine if a cell will start DNA synthesis. Because of this crucial role, any disruption of RB1 function can have significant effects on cell health and is associated with various human cancers. Besides its well-known role in halting the cell cycle, RB1 also affects how chromatin is organized, how genes are regulated, and how cells differentiate. These functions further underscore its importance in ensuring proper cell function.

The RB1 gene contributes to human cancer development primarily through genetic alterations. When RB1 is lost, it disrupts the control of the cell cycle, which can lead to tumor growth and progression [1,2]. Understanding how RB1 works is essential for cancer diagnosis, prognosis, and therapy development. This article aims to examine the role of RB1 gene changes in various human cancers beyond retinoblastoma. This review focuses on their biological effects, clinical importance, and potential impacts on cancer diagnosis and treatment. The RB1 gene produces the retinoblastoma protein (pRB), which regulates the cell cycle by inhibiting the transition from the G1 phase to the S phase.

II. MOLECULAR FUNCTIONS OF THE RB1 PROTEIN

The retinoblastoma protein (pRB), which is encoded by the RB1 gene, is a key tumor suppressor that functions in regulating the cell cycle, primarily at the G1/S checkpoint. In its hypophosphorylated active form, pRB binds and sequesters E2F transcription factors, thereby preventing them from activating genes required for DNA replication and S-phase entry. This interaction arrests cell cycle progression, ensuring

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that cells proliferate only in the presence of appropriate growth signals [3,4].

A. Cell Cycle Regulation and the E2F Pathway

Beyond controlling the G1/S transition, pRB regulates multiple E2F-dependent cellular processes that are crucial for cellular homeostasis [3,4] [Fig 1]. By binding to E2F transcription factors, pRB not only suppresses genes involved in DNA replication but also regulates the transcription of genes that control DNA repair, apoptosis, and cell differentiation [5,6]. This interaction ensures that cells with damaged DNA either repair the damage or undergo apoptosis, thereby preventing mutation accumulation. pRB also recruits chromatin-modifying complexes to E2F target promoters, which maintain transcriptional repression [4]. Loss of RB1 disrupts these regulatory networks and potentially leads to uncontrolled proliferation, an impaired DNA damage response, and evasion of apoptosis [1]. Thus, RB1 functions as a guardian of genomic integrity through its regulation of E2F-driven transcription along with cell cycle control.

B. RB1 in Apoptosis

The RB1 gene plays an important role in the regulation of apoptosis through its product, the retinoblastoma protein (pRB). pRB directly influences apoptotic signalling by modulating E2F transcription factors. The RB1 gene controls apoptosis through both E2F-dependent and E2F-independent mechanisms, acting as a condition-specific modulator of cell death. In addition, pRB modulates cellular sensitivity to apoptotic signals under stress conditions. In response to DNA damage, functional pRB regulates the intensity and duration of this response to prevent excessive or inadequate apoptosis [4,6]. Moreover, pRB interacts with chromatin-remodelling complexes and histone deacetylases to control the promoters of apoptosis-related genes, thereby maintaining survival in normal cells. Under severe genotoxic stress, phosphorylation or cleavage of pRB alters these interactions, enhancing the activation of mitochondrial apoptotic pathways. RB1 also interacts with the p53 pathway, promoting apoptosis when genomic damage is permanent. Loss of RB1 disrupts this regulatory balance; although unchecked E2F activity may temporarily promote apoptosis, tumor cells frequently acquire secondary alterations that bypass death signalling, resulting in apoptosis resistance and tumor progression [1]. Thus, RB1 serves as a critical controller of apoptotic sensitivity and cellular fate determination.

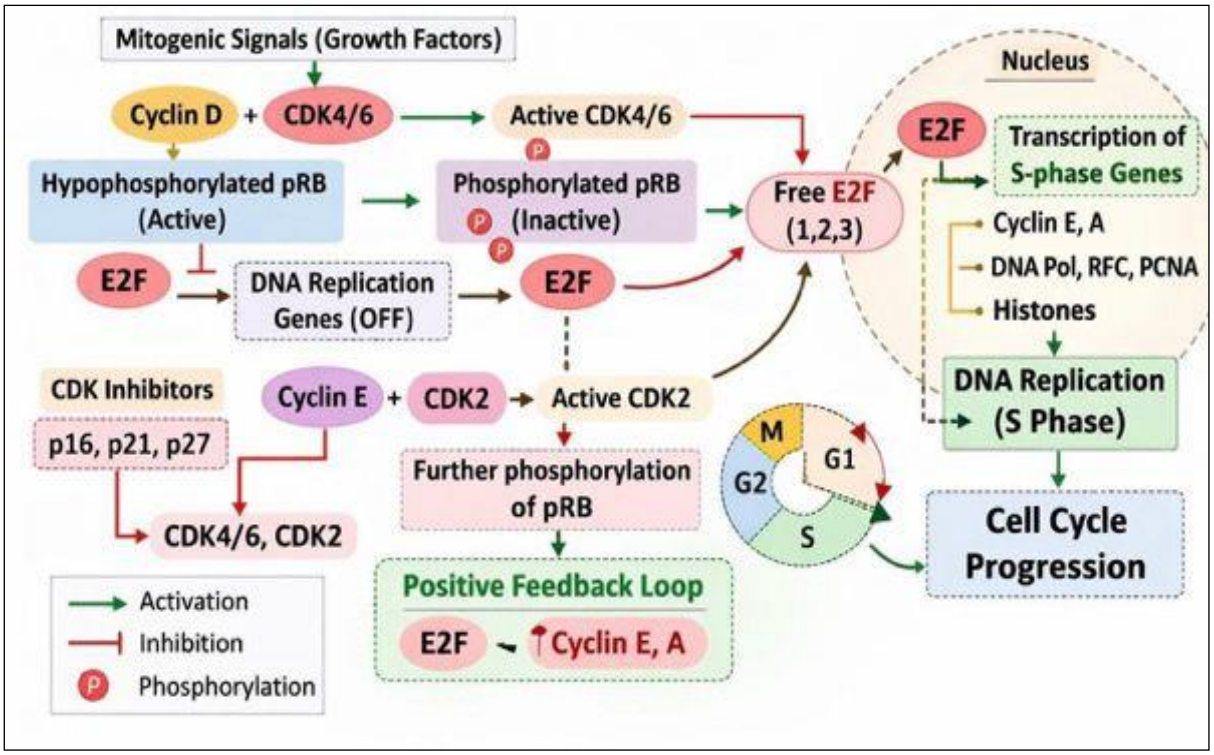

Fig. 1. E2F Pathway Regulating the G1-S Phase Transition.

C. Chromatin Structure and Epigenetic Regulation

Chromatin structure is continuously regulated to ensure precise gene expression, genome stability, and accurate progression of the cell cycle. The tumor suppressor Rb plays a major role in maintaining higher-order chromatin organization and promoting epigenetic states that control transcriptional repression. RB proteins interact with E2F transcription factors and recruit chromatin-modifying enzymes, which include histone deacetylases and histone methyltransferases, to launch repressive chromatin domains. These interactions lead to heterochromatin formation, especially at repetitive DNA regions and cell cycle–regulated promoters. Beyond controlling proliferation, the Rb family helps in long-term epigenetic memory by securing chromatin compaction and organizing histone modifications. Disruption of Rb function leads to altered chromatin architecture and epigenetic deregulation, increasing genomic instability and the risk of tumorigenesis. Thus, the Rb family blends cell cycle control with epigenetic mechanisms to preserve chromatin integrity and cellular identity [7].

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III. MECHANISMS OF RB1 LOSS IN TUMORIGENESIS

In sporadic and somatic cancers, RB1 inactivation occurs through point mutations, deletions, hypermethylation, or loss of heterozygosity. Epigenetic silencing through DNA methylation of the RB1 promoter is a non-mutational but functionally equivalent event that leads to gene inactivation. Additionally, viral oncoproteins such as HPV E7 can bind to and inactivate pRB, mainly in head and neck and cervical cancers. RB1 loss disrupts the G1/S checkpoint, permitting unchecked progression into the S phase and driving genomic instability [3]. This facilitates uncontrolled proliferation and enables the accumulation of further oncogenic mutations. In some tumors, RB1 loss also leads to therapeutic resistance, predominantly in neuroendocrine cancers. Hence, RB1 inactivation plays a dual role in initiating and sustaining tumorigenesis, making it a critical step in the development of several malignancies [1,2,8].

A. RB1 and Retinoblastoma

The RB1 gene plays a major role in the pathogenesis of retinoblastoma and various other cancers [8]. The disease occurs in hereditary and sporadic forms. Individuals inherit a germline mutation in one allele of the RB1 gene in hereditary cases. This makes all body cells carry this first “hit.” The second somatic mutation in a retinal cell leads to tumor formation [9,10]. These cases often present as bilateral and multifocal retinoblastoma; this carries an increased risk of developing other cancers such as osteosarcoma. In contrast, sporadic retinoblastoma arises when both mutations occur somatically in a single retinal cell, leading to a unilateral, unifocal tumor with no increased risk of secondary malignancies. This model of tumor development was explained by Alfred Knudson’s two-hit hypothesis (1971) [11].

B. RB1 Alterations in Human Cancers

Functional inactivation and mutations in the RB1 gene are observed across a wide variety of malignancies beyond retinoblastoma, highlighting its role as a tumor suppressor. In osteosarcoma, RB1 gene alterations are common in both sporadic cases and in individuals with hereditary RB1 mutations, particularly survivors of retinoblastoma, where loss of pRB function contributes to genomic instability, aggressive tumor behaviour, and poor prognosis [12]. In small cell lung carcinoma (SCLC), RB1 inactivation is one of the hallmark molecular events, alongside TP53 loss, driving uncontrolled proliferation, rapid tumor growth, early metastasis, and poor survival outcomes [13]. In bladder cancer, RB1 alterations (approximately 30–50%) are associated with tumor progression, higher-grade lesions such as muscle-invasive disease, and resistance to therapy [14]. In triple-negative breast cancer (TNBC), RB1 loss is observed in a subset of tumors and correlates with high proliferation rates, genomic instability, reduced response to certain drugs, and worse clinical outcomes [15]. Similarly, in advanced and castration-resistant prostate cancer (CRPC), RB1 loss promotes lineage plasticity and neuroendocrine differentiation, which contributes to resistance against androgen deprivation therapy and disease progression [16]. In glioblastoma, RB1 pathway disruption occurs in a tumor subset (around 10–15%), often through mutations or upstream pathway dysregulation, facilitating high-grade transformation by removing G1/S checkpoint control [17]. In melanoma, RB1 mutations are less common, but the RB1 pathway is frequently inactivated indirectly through CDK4/6 overactivity or loss of CDK inhibitors. This potentially leads to unchecked cell cycle progression and supports tumor growth and immune evasion [18]. In endometrial cancer, RB1 alterations occur in a subset of tumors and may cooperate with other mutations to promote proliferation and genomic instability [19]. In multiple myeloma, RB1 loss is more frequent, often due to chromosome 13q14 deletions affecting malignant plasma cells. This loss of pRB function leads to uncontrolled cell cycle progression and tumor growth [20].

C. Biological Consequences of RB1 Loss

Inactivation of RB1 has diverse biological and clinical consequences that extend beyond the loss of cell cycle control. Practically, the absence of active retinoblastoma protein leads to enhanced E2F transcriptional activity, driving continuous expression of genes involved in DNA synthesis and permitting replication and S-phase entry [3,4]. This deregulated transcriptional program enhances replicative stress and enables chromosomal instability, one of the hallmarks of cancer progression [2,8]. Cells that lack RB1 also exhibit defective checkpoint coordination, which allows proliferation despite DNA damage, thereby enhancing mutational burden and clonal evolution [5,6]. At the tissue level, loss of RB1 enhances tumor initiation and supports malignancy in different organ systems. It contributes to accelerated cell division and poorly differentiated phenotypes in aggressive cancers such as small cell lung carcinoma and triple-negative breast cancer [13,15]. In prostate cancer, RB1 deficiency increases lineage plasticity and neuroendocrine differentiation, enabling adaptation under therapeutic pressure [16]. From a therapeutic perspective, inactivation of RB1 alters drug responsiveness, as CDK4/6 inhibitors depend on functional pRB to mediate G1 arrest; RB1-deficient tumors demonstrate intrinsic resistance to these agents [21,22]. Furthermore, genomic instability associated with RB1 loss may influence tumor interactions and response rates to systemic therapies [2,22]. Altogether, RB1 inactivation influences genomic instability, tumor aggressiveness, phenotypic evolution, and treatment resistance across different malignancies.

IV. RB1 AS A BIOMARKER AND ITS THERAPEUTIC IMPLICATIONS

Loss of RB1 function leads to uncontrolled cell proliferation, and it also plays a crucial role as a biomarker in cancer diagnosis, prognosis, and therapeutic decision-making. As a main regulator of the G1/S checkpoint of the cell cycle, RB1 encodes the retinoblastoma protein (pRB), which inhibits uncontrolled proliferation by regulating E2F transcription factors [4]. Functional pRB is required for CDK4/6 inhibitors to exert their therapeutic effect. These agents prevent phosphorylation of pRB, which maintains it in an active growth-suppressive state and thereby induces cell cycle arrest. RB1 deletion, mutation, or functional inactivation, resulting in the absence or dysfunction of pRB, renders CDK4/6 inhibitors ineffective [3,5]. Hence, RB1 status works as a predictive biomarker for identifying patients likely to benefit from

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CDK4/6-targeted therapy and for predicting drug resistance and overall clinical outcomes [21,22]. As RB1 loss is implicated in rapidly progressive cancers such as triple-negative breast cancer, advanced prostate cancer, and small-cell lung carcinoma, it plays a major role in tumor progression, lineage plasticity, and therapeutic resistance [22,25]. RB1 inactivation accelerates genomic instability and tumor evolution. This instability can influence tumor–immune interactions, while the increased mutation burden can enhance neoantigen formation and potentially improve responses to immune checkpoint inhibitors in some cases. However, RB1-deficient tumors may also develop tumor evasion mechanisms, which include alterations in antigen presentation and changes in immune cell infiltration. Notably, RB1 alterations can be detected using liquid biopsy approaches such as circulating tumor DNA (ctDNA) analysis. This non-invasive technique helps in real-time monitoring of disease progression, clonal evolution, and therapeutic resistance [23]. The advancement of liquid biopsy technologies helps RB1 to be viewed as a dynamic biomarker that supports personalized therapy, rational combination strategies, and early adaptation of treatment plans. Thus, RB1 is not only a tumor suppressor gene involved in cell-cycle control but also a biomarker that helps in guiding personalized therapeutic approaches [21] – [26].

V. CONCLUSION

The tumor suppressor RB1, whose functional integrity is essential for maintaining controlled cell proliferation, genomic stability, and normal cellular differentiation, acts through the retinoblastoma protein (pRB). RB1 regulates the G1/S cell-cycle checkpoint by modulating E2F transcription factors and maintaining DNA replication, repair, and apoptosis. RB1 inactivation due to mutation, deletion, epigenetic silencing, or viral integration into the cell genome is an important event in the initiation and progression of various malignancies apart from retinoblastoma, including osteosarcoma, small cell lung cancer, bladder cancer, triple-negative breast cancer, prostate cancer, glioblastoma, melanoma, endometrial cancer, and multiple myeloma. Inactivation or loss of RB1 is strongly linked with aggressive tumor behaviour, lineage plasticity, therapeutic resistance, and poorer outcomes in several cancers. As recent studies show, RB1 status acts as a valuable predictive biomarker, particularly in guiding the use of CDK4/6 inhibitors and in understanding pathways of therapeutic failure. Advances in liquid biopsy techniques enable RB1 to be evaluated as a dynamic biomarker for assessing tumor evolution. Overall, understanding RB1 mechanisms is a key principle in precision oncology, and facilitating the development of more effective individualized cancer therapies.

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