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Review Article

The *RB* Epigenetic Functions in Cancer Progression Control

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The findings that the retinoblastoma tumor suppressor gene product (pRB) controls gene expression by physically interacting with several epigenetic regulators reveals another potential form of the *RB* functions in global regulation of the epigenome beyond its well known functions in regulation of the E2F and tissue specific transcription factors. This plethora of novel *RB* functions may explain why *RB* should be inactivated in the vast majority of human cancers, and will provide insights for better understanding the future rationale for the epigenetic therapy of cancers.

The human retinoblastoma (*RB*) gene was the first tumor suppressor gene identified 26 years ago [1]. Since then numerous studies have characterized the role of pRB-E2F interaction in the control of G1-S transition of the cell cycle. Later research delineated the role of *pRB* interaction with tissue specific transcription factors in regulation of terminal differentiation. *RB* function is inactivated in most if not all of human cancers either through *RB* gene mutation or more commonly, through deregulation of pRB regulators such as cyclin D-CDK complexes and p16^{INK4A} resulting in deregulated phosphorylation of pRB. Inactivation of pRB is frequently detected during tumor progression and is implicated in many facets the malignant phenotype [2]. In addition, pRB was demonstrated to antagonize cancer progression by regulating the DNA damage response (DDR) signaling and cellular senescence [3]. These observations suggest that *pRB* exhibits more functions beyond its appreciated role in the control of cell cycle and differentiation [2,4].

Functional pRB does repress gene transcription not only by sequestering transcription factors away from their DNA binding consensus sequences but also by recruitment of epigenetic modifiers to gene promoters. Therefore, pRB is functioning like double-sided adhesive tape interacting with sequence-specific DNA-binding proteins on one side and epigenetic modifiers on the other side. Consequently, *RB* inactivation deregulates various cellular mechanisms orchestrating global genomic and epigenomic activities. Previous studies confirmed that pRB physically interact with several epigenetic modifiers including histone deacetylase (HDAC), DNA methyltransferase-1 (DNMT1), heterochromatin protein-1 (HP1) and suppressor of variegation 3-9 homolog-1(Suv39h1) [5,6] and recruit them into gene promoters however; the precise mechanism and target genes of the pRB epigenetic function are still largely unknown. Epigenetic aberrations particularly in the DNA methylation pattern critically

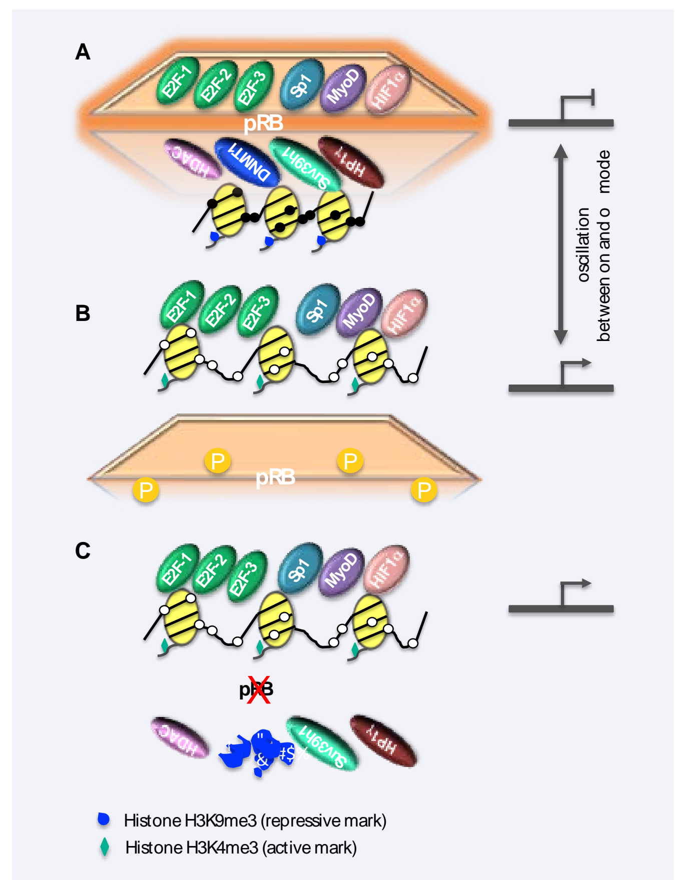

Figure 1 **pRB functions in regulation of global DNA methylation and chromatin modifications. A.** pRB is hopophosphorylated and functions like double-sided adhesive tape with sequence-specific DNA-binding transcription factors bound to one side away from their DNA binding consensus sequences, and epigenetic modifiers recruited by the other side inducing DNA methylation and histone modifications that result in tanscription repression. **B.** When pRB is hypermethylated, sequence-specific DNA-binding transcription factors are released and bind to their consensus DNA binding sites inducing DNA methylation and histone modifications that result in transcription activation. In normal cells (A and B), functional pRB flips the genome and epigenome activities as required. **C.** Unavailability of pRB leaves the sequence-specific DNAbinding transcription factors freely binding to their consensus DNA sites inducing DNA methylation and histone modifications that result in sustained transcription activation. We reported that loss of pRB induces ATM activation and DNMT1 degradation leading to DNA hypomethylation [7]. Also, in absence of pRB the chromatin is constantly open and easily accessible by its binding partners.

associate with cancer progression. We recently reported that inactivation of the pRB pathway in coordination with aberration in the DDR deregulates DNMT1 protein stability leading to promoter localized abnormal DNA methylation pattern and malignant progression of the C (calcitonin producing) cell tumors developed in $Rb^{+/-}$ mice [7]. Furthermore, previous study indicated that primary human retinoblastomas harbor mutations only in the *RB* gene, and demonstrated promoter localized epigenetic alterations rather than chromosomal instability (CIN) as a mechanism underlying the malignant progression in these tumors [8].

pRB inactivation plays a certain role in the nuclear reprogramming of embryonic stem (ES) cells, induced pluripotent stem (iPS) cells, mouse embryonic fibroblasts (MEFs) and tumor cells [9-13] assigning a crucial role for the *RB* function in development, regenerative medicine and cancer. Our previous study demonstrated the mechanism by which pRB functions coordinate DNA damage signaling and DNA methylation via regulation of the ATM-Tip60-DNMT1 interaction [7]. Most recently another group reported that ATM-Tip60 interaction couples DNA damage signaling to chromatin modifications [14]. Taken together these observations highlight novel pRB functions in regulation of the epigenetic control of cancer progression. Genome-wide DNA methylation profiling along with comparative analyses of histone modifications, mRNA and small RNA by the next generation sequencing technologies would enable us to determine critical epigenetic alterations induced by *RB* loss in human cancers. These expectations empower us to appraise the future rationale for epigenetic therapy of human cancers.

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