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Preface

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Cancer is a genetic disease, requiring alterations of tumor suppressor genes and proto-oncogenes that may occur due to intrinsic factors or exogenous agents. The mechanisms of malfunction in tumor suppressor genes and proto-oncogenes are different. Tumor suppressors are inactivated by 'loss-of-function' mutations, whereas proto-oncogenes are activated through 'gain-of-function' mutations. Concisely, tumor suppressors are functionally compromised in cells, thus causing the loss of control over homeostasis. On the other hand, proto-oncogenes are constitutively activated, leading to continuous signaling which acts positively on cell growth. Despite these different mechanisms for altering gene function, disrupting the regulatory balance, which maintains homeostasis is an essential step toward carcinogenesis. The magnitude by which this balance is disrupted depends on the essentiality of the genes in a given regulatory pathway. In general, malfunction of a tumor suppressor gene can result from mutation either in both alleles or a single allele, while proto-oncogene-driven transformation may require the mutation of only a single copy of the proto-oncogene leading toward cellular transformation.

In this issue of the review, we focus on the recent progress of the first-identified human tumor suppressor gene, the retinoblastoma gene (RB). RB is the prototypical tumor suppressor and is recognized through the hereditary RB family. In the late 1980s, the RB gene and protein were identified at the molecular level, and soon after it was realized that RB has a much broader role in human carcinogenesis than simply in the eye. The discovery of RB is one of the critical milestones in cancer research. In addition to RB, pRB2/p130 and pRBL1/p107 were subsequently identified as highly related RB homologs forming the RB gene family.

During the past two decades, significant efforts have been made to elucidate the fundamental function of RB in cancer suppression. The RB proteins have no known enzymatic activity but serve as an adaptor protein in coordinating several critical regulatory pathways. RB plays an essential role in cell cycle progression: association with E2F factors to control the G1 restriction point and with other factors guarding S phase progression, as well as modulating essential factors for mitotic chromosome segregation. Moreover, RB is vital for terminal differentiation for many cell lineages by chaperoning their respective transcription factors. These fundamental functions explain how RB maintains homeostasis in cells and organisms during the developmental process.

RB protein is subjected to different secondary modifications in order to adapt itself to those diverse biological functions. The most prominent modification is phosphorylation and dephosphorylation. A group of kinases including cyclin-dependent kinases and ERK kinases plays an essential role in regulating RB function. Phosphatases are also important in this regard. RB may interact with distinctive partners through different forms of RB. Matching this specific modification to a given RB function is challenging and interesting. Similarly, other modes of modification of RB may have specific biological function. It is expected that similar regulatory modification will occur in the rest of the RB family proteins.

After all, the importance of the tumor suppressor genes is to be able to apply them in cancer management. Beyond providing a useful biomarker for diagnosing cancer, replacement with an active wild-type allele of the tumor suppressor gene may offer a novel treatment. Indeed, reconstitution with a wild-type allele of RB enables suppression of tumorigenecity in retinoblastoma, osteosarcoma, and many RB-deficient tumors. Its role as a tumor suppressor was demonstrated not only in a xenografted animal system, but also in RB knockout heterozygous mice that were prone to tumor formation resulting from inactivation of RB. This preclinical experiment provided the first prototypical study for the therapeutic application of tumor suppressor genes in humans.

pRB2/p130 and pRBL1/p107 have significant homologies with RB but cannot substitute for RB. Their distinct functions in cancer suppression are intriguing. Besides their central responsibility for the RB family proteins, exploring their specific associations with a vast number of nuclear proteins bearing various kinds of functions in numerous pathways is a daunting task. Elucidating the combination of those diverse functions of RB family proteins in different cellular processes will provide a blueprint for understanding how cell cycle proceeds and how cells differentiate.

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