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IN PERSPECTIVE

The *Rb* Family Connects With the *Tp53* Family in Skin Carcinogenesis

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In contrast with the low frequency of alterations found in the *Rb* gene, the pRb pathway is inactivated in the vast majority of human tumors. A similar situation takes place in mouse models of cancer, including two-stage skin tumorigenesis. This might be explained if the *Rb* functions are carried out, in its absence, by other proteins that are also controlled by the same upstream regulators and display similar effectors. The other Rb family members, p107 and or p130, are plausible candidates. The embryonic lethality of pRb-deficient animals, which precludes the analysis of the roles of *Rb* gene in mouse models, has been avoided using tissue-specific deletion of pRb. In epidermis, pRb deletion leads to altered proliferation and differentiation. However, these deficient mice do not develop spontaneous tumors, and chemical carcinogenesis experiments revealed that the absence of pRb renders fewer and smaller tumors than control animals, but showing increased malignant conversion to squamous cell carcinomas (SCC). Detailed biochemical analyses have indicated that, in the absence of pRb, multiple pathways, including the aberrant p53 activation mediated by E2F/p19^{ARF}, are activated leading to increased tumor apoptosis. As *Rb* loss in epidermis is functionally compensated by *Rbl1* (p107), this might also suggest that p107 could behave as a tumor suppressor. We summarize here our findings in support of this hypothesis. The pRb−; p107−/− epidermis form spontaneous tumors, and the reduction of p107 levels restores the susceptibility of pRb-mice to chemical skin carcinogenesis experiments. Moreover, *Rb*-deficient keratinocytes are highly susceptible to Ha-ras-induced transformation, and this susceptibility is enhanced by p107 loss. Further functional studies have indicated that the loss of p107 in the absence of pRb produces the reduction of p53-dependent proapoptotic signals through the modulation of p63 and p73 isoforms. In addition, expression profiling analysis has revealed multiple oncogenic alterations that can contribute to tumor susceptibility in epidermis in the absence of pRb and p107.

Key words: mouse skin carcinogenesis; pRb; p107; cell cycle; apoptosis; signal transduction; p53; p63; p73; microarray

INTRODUCTION

Tumor cells arise, initially, by genomic alterations, in most cases somatic, affecting primarily oncogenes, tumor suppressor genes, and/or DNA repair genes. These alterations allow tumor cells to acquire new characteristics that differentiate them from the normal cell population. These include uncontrolled proliferation, altered differentiation, antiapoptotic activities, and the acquisition of properties to alter the tumor environment to obtain the required nutrients, and to attain the functions that ultimately will allow them to invade and damage surrounding tissues and organs forming metastasis. All these processes that take place in tumor cells share multiple and intricate connections at the molecular level.

The molecular mechanisms controlling cell proliferation involve two major connected frameworks: the signal transduction cascades, which drive the information from the environment to the intimate cell control processes, and the cell cycle, which controls that cell division proceeds in an ordered and accurate manner depending on the external signals. Both are highly controlled processes modulated at different levels: gene expression to ensure that the required proteins are present at the necessary levels in the precise time, and posttranscriptional events, which include proteolysis, intracellular transport and localization, and mechanisms that allow the reversible activation/inactivation of certain key proteins. This last aspect is primarily exerted by phosphorylation–dephosphorylation mechanisms carried out by kinases and phosphatases.

The mouse cancer models are essential tools to analyze the molecular mechanisms that take place during carcinogenesis. They allow the analysis of specific tumor genetics, the close analysis of tumor pathology, and the identification and validation of putative therapeutic targets. The two-stage mouse skin carcinogenesis is perhaps the best characterized system and represents a suitable model to understand the multistage nature of tumorigenesis. In this

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