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BRIEF COMMUNICATION

Susceptibility of pRb-Deficient Epidermis to Chemical Skin Carcinogenesis Is Dependent on the p107 Allele Dosage

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Functional inactivation of the pRb-dependent pathway is a general feature of human cancer. However, only a reduced spectrum of tumors displays inactivation of the *Rb* gene. This can be attributed, at least partially, to the possible overlapping functions carried out by the related retinoblastoma family members p107 and p130. We observed that loss of pRb in epidermis, using the Cre/LoxP technology, results in proliferation and differentiation defects. These alterations are partially compensated by the elevation in the levels of p107. Moreover, epidermis lacking pRb and p107, but not pRb alone, develops spontaneous tumors, and double deficient primary keratinocytes are highly susceptible to Ha-ras-induced transformation. Two-stage chemical carcinogenesis experiments in mice lacking pRb in epidermis revealed a reduced susceptibility in papilloma formation and an increase in the malignant conversion. We have now explored whether the loss of one p107 allele, inducing a decrease in the levels of p107 up to normal levels could restore the susceptibility of pRb-deficient skin to two-stage protocol. We observed partial restoration in the incidence, number, and size of tumors. However, there is no increased malignancy despite sustained p53 activation. We also observed a partial reduction in the levels of proapoptotic proteins in benign papillomas. These data confirm our previous suggestions on the role of p107 as a tumor suppressor in epidermis in the absence of pRb.

Key words: skin; epidermis; tumorigenesis; retinoblastoma; p107; Ras; Tp53; proliferation; apoptosis

INTRODUCTION

The retinoblastoma protein (pRb) integrates different signaling cascades to modulate cell cycle progression, differentiation and inhibition of oncogenic transformation in multiple tissues [1]. pRb regulates transcriptional processes through binding to transcription factors, best illustrated by the inhibition of E2F family members [2]. Cell proliferation requires functional inactivation of pRb via progressive phosphorylation by different cyclin–cyclin dependent kinase complexes, also controlled by members of cyclin dependent kinase inhibitors [3,4]. Remarkably, the vast majority of human tumors displayed alterations in any of the elements of this pathway, whereas specific inactivation of *Rb* is restricted to specific tumor subsets [5–7].

The skin carcinogenesis system has been used to show the role of specific oncogenic events in tumorigenesis. Classically, the DMBA application produces mutations in the *Ha-ras* gene that, upon hyperproliferative stimulation, leads to the generation of papillomas, which in most cases regress, but in some cases evolve to squamous cell carcinomas (SCC). The roles of cyclin D [8], cdk4 [9,10], ckis [11], and E2F members [12] have indicated the involvement of the pRb pathway in this system. More recently, using the epidermal-specific ablation of *Rb* gene [13], we tested the pRb functions in two-stage chemical carcinogenesis [14]. Our data revealed that the absence of pRb leads to reduced tumor development due to increased p53-dependent apoptosis. However, the pRb-deficient tumors displayed increased malignant conversion associated with changes in specific signal transduction pathways [14,15].

We have also explored the possibility that the other Rb family members can act as tumor suppressors

Abbreviations: SCC, squamous cell carcinomas; BrdU, bromodeoxyuridine.

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