Published in final edited form as:
Oncogene. 2014 September 11; 33(37): 4599–4612. doi:10.1038/onc.2013.417.

p21 suppresses inflammation and tumorigenesis on pRB-deficient stratified epithelia

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Abstract

The retinoblastoma gene product (pRb) controls proliferation and differentiation processes in stratified epithelia. Importantly, an in contrast to other tissues, *Rb* deficiency does not lead to spontaneous skin tumor formation. As the cyclin dependent kinase inhibitor p21 regulates proliferation and differentiation in the absence of pRb, we analyzed the consequences of deleting p21 in pRb-ablated stratified epithelia (hereafter $pRb^{\Delta Epi}$;p21-/-). These mice display an enhancement of the phenotypic abnormalities observed in $pRb^{\Delta Epi}$ animals, indicating that p21 partially compensates pRb absence. Remarkably, $pRb^{\Delta Epi}$;p21-/- mice show an acute skin inflammatory phenotype and develop spontaneous epithelial tumors, particularly affecting tongue and oral tissues. Biochemical analyses and transcriptome studies reveal changes affecting multiple pathways, including DNA damage and p53-dependent signaling responses. Comparative metagenomic analyses, together with the histopathological profiles, indicate that these mice constitute a faithful model for human head and neck squamous cell carcinomas. Collectively, our findings demonstrate that p21, in conjunction with pRb, plays a central role in regulating multiple epithelial processes and orchestrating specific tumor suppressor functions.

Introduction

The pocket protein family (pRb, p107 and p130) plays unique and overlapping roles in differentiation and cell cycle control (1). Of them, the *Rb* gene is the predominant family member mutated in human tumors. This reflects the essential role of pRb in the control of

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