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RESEARCH ARTICLE

Functional Link Between Retinoblastoma Family of Proteins and the Wnt Signaling Pathway in Mouse Epidermis

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The retinoblastoma family of proteins (pRb, p107, and p130) modulates cell cycle progression and differentiation of several tissues. We have demonstrated recently that p107 and p130 regulate keratinocyte terminal differentiation and hair follicle morphogenesis and development in vivo. This last aspect appears to be mediated by defective signaling from the mesenchyme and is associated with altered bone morphogenetic protein-4 (BMP4) -dependent signaling. However, many alterations were also found in the epithelial compartment. Given the importance of βcatenin in hair biology and in BMP signaling, we studied its expression in p107/p130-deficient skin. Although normal expression of βcatenin was found in p107/p130-deficient hair follicles, we found increased nuclear accumulation of βcatenin in the basal keratinocytes of the p107/p130-deficient mice skin. Biochemical analysis revealed that such an increase in βcatenin was due to the disruption of Axin/GSK3β/βcatenin complexes promoted by the increased expression of Frat, the mouse homologue of GSK3βbinding protein (GBP), in epidermis, precluding the degradation of βcatenin. Collectively, these data represent the first evidence that retinoblastoma family and Wnt signaling pathways might be interconnected by functional links in skin. *Developmental Dynamics 230:410–418, 2004.* © 2004 Wiley-Liss, Inc.

Key words: epidermis; hair follicle; βcatenin; Frat; retinoblastoma; Lef/TCF

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INTRODUCTION

The retinoblastoma family of proteins (pRB, p107, p130) modulates the G_1 to S phase transition (Weinberg, 1995). Besides their functions as negative modulators of cell cycle progression, the proteins of the retinoblastoma family modulate different aspects of differentiation such as clonal expansion, permanent cell cycle withdrawal, and induction of tissue-specific gene expression (reviewed in Lipinski and Jacks, 1999). Most of these aspects have been inferred from the data obtained in mice lacking the different members of the retinoblastoma family. pRb-deficient animals die between day 13 and 15 of gestation, displaying overt defects in erythroid, neuronal, and lens development (Clarke et al., 1992; Jacks et al., 1992; Lee et al., 1992). However, recent data obtained using tissue-specific ablation of *Rb* gene have suggested that these defects are due to a non-cell autonomous effect rather than direct effects in neurons and erythropoiesis (MacPherson et al., 2003; Wu et al., 2003). Mice deficient in p107 or p130 develop normally and do not display any overt phenotype (Cobrinik et al., 1996; Lee et al., 1996), indicating that, in most of the tissues, either p107 or p130 are dispensable for development, suggesting a functional overlap between them. In agreement, mice lacking both proteins die immediately after birth and display shortened limbs and defects in bone development, associated with impaired chondrocyte differentiation (Cobrinik et al., 1996). Of interest, it has been reported that the genetic background may determine the developmental consequences of p107 or p130 deficiency (LeCouter et al., 1998a,b).

Mammalian skin is composed of three different epithelial compart-

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