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Constitutively Active Akt Induces Ectodermal Defects and Impaired Bone Morphogenetic Protein Signaling

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Aberrant activation of the Akt pathway has been implicated in several human pathologies including cancer. However, current knowledge on the involvement of Akt signaling in development is limited. Previous data have suggested that Akt-mediated signaling may be an essential mediator of epidermal homeostasis through cell autonomous and noncell autonomous mechanisms. Here we report the developmental consequences of deregulated Akt activity in the basal layer of stratified epithelia, mediated by the expression of a constitutively active Akt1 (myrAkt) in transgenic mice. Contrary to mice overexpressing wild-type Akt1 (Akt^{wt}), these myrAkt mice display, in a dose-dependent manner, altered development of ectodermally derived organs such as hair, teeth, nails, and epidermal glands. To identify the possible molecular mechanisms underlying these alterations, gene profiling approaches were used. We demonstrate that constitutive Akt activity disturbs the bone morphogenetic protein-dependent signaling pathway. In addition, these mice also display alterations in adult epidermal stem cells. Collectively, we show that epithelial tissue development and homeostasis is dependent on proper regulation of Akt expression and activity.

INTRODUCTION

A large number of processes in the cell are modulated by the protein kinase Akt, also known as protein kinase B (PKB). In particular, this kinase has been widely involved in the control of cell survival and apoptosis, proliferation, cell cycle progression, glucose metabolism, and protein translation (Brazil *et al.,* 2004). Three Akt isoforms sharing common structural features (Hanada *et al.,* 2004) have been found in mammals (Akt1, Akt2, Akt3). Although the relevance of Akt signaling in cancer is widely recognized (Bellacosa *et al.,* 2005; Manning and Cantley, 2007), its involvement in development has only recently been highlighted. Akt1 and Akt2 knockout (KO) mice are viable and exhibit mild phenotypes characterized by growth retardation and diabetes (Chen *et al.,* 2001; Cho *et al.,* 2001), suggesting functional redundancy among Akt isoforms. Further proof of these overlapping roles comes from analysis of compound mutant mice. Akt1 and Akt2 double KO mice displayed a much more severe phenotype: dwarfism, impaired skin development, delayed bone development, reduced adipogenesis, and early lethality after birth (Peng *et al.,* 2003). More recently, mice with combined mutant alleles of Akt1 and Akt3 have also been generated. Double KO of Akt1 and Akt3 causes embryonic lethality at around embryonic days 11 and 12, and Akt1−/−;Akt3−/− mice have severe developmental defects in the cardiovascular and nervous systems (Yang *et al.,* 2005). Akt1−/−;Akt3+/− mice display multiple defects in the thymus, heart, and skin and die within several days after birth, whereas Akt1+/−;Akt3−/− mice are viable (Yang *et al.,* 2005). These data demonstrate that the three Akt isoforms have overlapping functions but also may have unique functions in specific organs.

Besides the skin phenotype observed in different compound-deficient mice, several lines of evidence have highlighted the importance of the phophoinositide 3 kinase (PI3K)/Akt pathway in epidermis. Of particular interest is the relevant role of Akt during mouse skin carcinogenesis. We have demonstrated that Akt is a key molecule in insulin growth factor 1 (IGF-1)-mediated mouse skin tumor promotion (Wilker *et al.,* 2005). In addition, Akt exerts essential roles in two-stage carcinogenesis protocols affecting tumor proliferation and apoptosis (Segrelles *et al.,* 2002) and also modulates the tumor-stroma cross-talk leading to an increase in angiogenesis (Segrelles *et al.,* 2004). Recently, using cultured cell systems, we provided evidence indicating that the functions of Akt in epidermal tumors are exerted by transcriptional and posttranscriptional mechanisms and

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Abbreviations used: BMP, bone morphogenetic protein; HF, hair follicle.