Deregulated Activity of Akt in Epithelial Basal Cells Induces Spontaneous Tumors and Heightened Sensitivity to Skin Carcinogenesis

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Abstract

Aberrant activation of the phosphoinositide-3-kinase (PI3K)/PTEN/Akt pathway, leading to increased proliferation and decreased apoptosis, has been implicated in several human pathologies including cancer. Our previous data have shown that Akt-mediated signaling is an essential mediator in the mouse skin carcinogenesis system during both the tumor promotion and progression stages. In addition, overexpression of Akt is also able to transform keratinocytes through transcriptional and posttranscriptional processes. Here, we report the consequences of the increased expression of Akt1 (wtAkt) or constitutively active Akt1 (myrAkt) in the basal layer of stratified epithelia using the bovine keratin K5 promoter. These mice display alterations in epidermal proliferation and differentiation. In addition, transgenic mice with the highest levels of Akt expression developed spontaneous epithelial tumors in multiple organs with age. Furthermore, both *wtAkt* and *myrAkt* transgenic lines displayed heightened sensitivity to the epidermal proliferative effects of the tumor promoter 12-*O*-tetradecanoylphorbol-13-acetate (TPA) and heightened sensitivity to two-stage skin carcinogenesis. Finally, enhanced susceptibility to two-stage carcinogenesis correlated with a more sustained proliferative response following treatment with TPA as well as sustained alterations in Akt downstream signaling pathways and elevations in cell cycle regulatory proteins. Collectively, the data provide direct support for an important role for Akt signaling in epithelial carcinogenesis *in vivo*, especially during the tumor promotion stage. [Cancer Res 2007;67(22):10879–88]

Introduction

Akt is a 60-kDa serine/threonine kinase capable of modulating numerous processes in the cell, including cell survival and apoptosis, proliferation, cell cycle progression, glucose metabolism, and protein translation through numerous downstream signaling proteins (1). Well-characterized substrates of Akt include anti-apoptotic proteins, such as Foxo, BAD, and IKK-β; cell cycle regulators, such as p27kip1, p21cip1, MDM2, and Myt1; and GSK-3, which is involved in a variety of processes (1). There are three Akt isoforms in mammals (Akt1, Akt2, and Akt3). They all share common structural features with three functionally distinct regions: an NH_2-terminal pleckstrin homology domain, a catalytic domain in the center, and a COOH-terminal hydrophobic motif (2).

Data generated over the past decade have shown that the activation of Akt kinases is frequent in a wide number of human solid tumors and hematologic malignancies (reviewed in ref. 3). In addition, several mouse models have contributed to our understanding that aberrant Akt signaling plays a predominant role in malignant transformation *in vivo*, either alone or in cooperation with other genetic alterations (4–6). We have shown that Akt is a key molecule in insulin-like growth factor-I (IGF-I)–mediated mouse skin tumor promotion (7). In addition, diverse tumor promoters have been shown to activate epidermal Akt following topical treatment through activation of the EGFr (8). Furthermore, we have shown that Akt exerts tumor-specific effects in response to two-stage carcinogenesis protocols by modulating proliferation and apoptosis (9), and Akt also influences the tumor-stroma relationship by enhancing angiogenesis (10). Recently, using cultured cell systems, we provided evidence indicating that Akt may function differently in epidermal tumors than in other tissues through transcriptional and posttranscriptional mechanisms, which have several parallels with human head and neck squamous cell carcinomas (SCC; ref. 11).

To further explore the role of Akt in skin, we generated transgenic mice that express either a wild-type form of *Akt1* (wtAkt), or a form that is permanently activated by means of a myristoylation sequence (myrAkt), directed to the basal layer of the stratified epithelia using the *bovine K5* (*BK5*) promoter. We show here that deregulated expression of Akt and, concomitantly, increased Akt activity lead to the development of spontaneous tumors in multiple tissues of founders or lines with the highest expression levels. In addition, expression of either wtAkt or myrAkt in epidermal basal cells dramatically enhances susceptibility to two-stage skin carcinogenesis. Collectively, the data show that deregulated expression of Akt and the accompanying alterations in signaling pathways and gene expression can lead to spontaneous tumor development and an enhanced response to chemical carcinogenesis in the skin.

Note: Supplementary data for this article are available at Cancer Research Online (http://cancerres.aacrjournals.org/).

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