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Review

Critical role of IκB kinase alpha in embryonic skin development and skin carcinogenesis

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Summary. IκB kinase alpha (IKKα), IKKß, and IKKγ/NEMO form the IKK complex, which is essential for NF-κB activation. However, genetic studies have shown that the role of IKKα is distinct from that of IKKß or IKKγ in the development of the mouse embryonic skin. Loss of IKKα has been shown to cause epidermal hyperplasia, prevent keratinocyte terminal differentiation, and impair the formation of the skin, resulting in the deaths of IKKα-deficient ($Ikk\alpha^{-/-}$) mice soon after birth. Recent experimental data from several laboratories have revealed that IKKα functions as a tumor suppressor in human squamous cell carcinomas (SCCs) of skin, lungs, and head and neck. Chemical carcinogenesis studies using mice have shown that reduction in IKKα expression increases the number and size of Ras-initiated skin tumors and promotes their progression, indicating that reduced IKKα expression provides a selective growth advantage that cooperates with Ras activity to promote skin carcinogenesis. In this review, we will summarize these findings from our and other studies on the role that IKKα plays in development of the mouse embryonic skin and skin carcinogenesis.

Key words: IκB kinase alpha (IKKα), Embryonic skin development, Skin carcinogenesis, Nuclear factor-kappaB (NF-κB)

IKKα/CHUK polypeptide

IKKα (previously known as CHUK) was identified as a kinase for inhibitor of NF-κB (IκBs) in 1997 (Connelly and Marcu, 1995; Mock et al., 1995; DiDonato et al., 1997; Mercurio et al., 1997). It is an 85-kDa polypeptide with 745 amino acids (aa) and contains a putative kinase catalytic domain (KD, 15-300 aa) with all 12 regions of homology characteristic of protein serine/threonine kinases, a leucine zipper (LZ) motif, and a helix-loop-helix (HLH) motif. IKKα is a classic zipper protein, like c-myc, Id1, C/EBP, and Jun, containing both LZ and HLH motifs (Connelly and Marcu, 1995). Notably, 30% of the polypeptide sequences in the LZ of IKKα are identical to those in the LZ of c-myc that plays an important role in regulating cell growth. Because IKKα has multiple domains, it likely serves multiple functions in diverse intercellular processes.

IKKß is an 87-kDa polypeptide with a structure similar to that of IKKα (Mercurio et al., 1997; Zandi et al., 1997). IKKα and IKKß have extensive sequence similarities: 62% in the KD, 67% in the LZ motif, and 40% in the HLH motif. Both IKK subunits are able to form homodimers and heterodimers through their LZ and HLH motifs. The dimerization is required for their kinase activity and for their own stabilization (Zandi et al., 1997, 1998). The C-terminal regions of IKKα and IKKß interact with IKKγ to form the IKK complex, a major kinase, which phosphorylates IκBs that bind to NF-κB in the cytoplasmic compartment, preventing NF-κB activation (Rothwarf et al., 1998; Yamaoka et al. 1998; May et al., 2000; Hu et al., 2001). IκB phosphorylation leads to its degradation, which allows NF-κB to translocate from the cytoplasm to the nucleus, where it functions as transcriptional factors for many genes. Many NF-κB targets are involved in inflammation, immunity, apoptosis, and cell cycle regulation. *In vitro* chemical studies have shown that IKKß has a stronger kinase activity than IKKα for IκBs

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Abbreviations: IKK, IκB kinase; IKKα, IκB kinase alpha; NF-κB, nuclear factor-κB; IκB, nuclear factor-κB inhibitor; NEMO, nuclear factor-κB essential modulator; DMBA, 7,12-dimethylbenz[a]anthracene; TPA, 12-O-tetradecanoylphorbol-13-acetate; EGF, epidermal growth factor; HB-EGF, heparin-binding EGF; FGF, fibroblast growth factor; VEGF, vascular endothelial growth factor; TNFα, tumor necrosis factor alpha; BrdU, Bromodeoxyuridine; IL-1, interleukin-1

(Zandi et al., 1997). A C-terminal-80-aa deletion in IKKα that contains the IKKγ binding site did not affect the IKKα kinase activity (Hu et al., 2001). Based on their similarities in structural features and biochemical activities, IKKα and IKKß were assumed to be functionally redundant *in vivo*. However, genetic studies have revealed that IKKß and IKKγ, but not IKKα, are upstream activators of NF-κB in mice (Li et al., 1999b; Li et al., 1999; Makris et al., 2000). IKKα-deficient ($Ikk\alpha^{-/-}$) mice exhibited major phenotypes in skin development different from those in $Ikk\beta^{-/-}$ and $Ikk\gamma^{-/-}$ mice (Hu et al., 1999; Li et al., 1999a; Takeda et al., 1999). Also, the skin of $Ikk\alpha^{-/-}$ mice preserved IKK and NF-κB activities (Hu et al., 2001). Thus, although IKKα and IKKß have similar biochemical activities in phosphorylating IκBs, they have different physiological functions.

Role of IKKα in development of mouse embryonic skin

Skin is composed of the epidermis and the dermis. Keratinocytes constitute the epidermis. Epidermal basal keratinocytes are mitotic. After moving to the suprabasal layers, the keratinocytes gradually differentiate and give rise to the tough, soft cornified layers at the top of the skin that protects the internal organs. Before embryonic day 12 (E12), mouse embryos have only one cell layer in the epidermis; after E16, terminally differentiated keratinocytes in multiple epidermal layers can be observed. Basal epidermal keratinocytes express keratin 5 (K5) and K14; the intermediately differentiated keratinocytes express K1 and 10; the terminally differentiated keratinocytes express the markers filaggrin and transglutaminase (Fuchs and Byrne, 1994).

E12 $Ikk\alpha^{-/-}$ mouse embryos are indistinguishable from wild-type (WT) embryos (Hu et al., 1999). After E12.5 day, the epidermis of the body and limbs in $Ikk\alpha^{-/-}$ embryos starts to gradually fuse together, so that the development of the limbs is covered under a skin sheet. $Ikk\alpha^{-/-}$ mice look like pupae at birth, and they die soon after birth due to severely impaired skin. Electron microscopy revealed no terminally differentiated keratinocytes in the epidermis of the IKKα deficient mouse embryos (Hu et al., 1999). The entire epidermis of $Ikk\alpha^{-/-}$ newborn mice expressed K5 and K14 and contained increased bromodeoxyuridine (BrdU) stained-positive cells, an S phase indicator, but did not express the terminal differentiation marker filaggrin. These results suggest that loss of IKKα promotes keratinocyte proliferation, prevents keratinocyte terminal differentiation, and severely impairs skin formation (Fig. 1). Thus, IKKα is essential for the development of the embryonic skin and the shape of the body.

Primary cultured $Ikk\alpha^{-/-}$ keratinocytes formed larger colonies than did WT keratinocytes and did not express filaggrin (Hu et al., 2001). In response to stimulation with either tumor necrosis factor-α (TNFα) or interleukin-1 (IL-1), IKK and NF-κB DNA binding activities were higher in $Ikk\alpha^{-/-}$ than in WT keratinocytes, which was likely due to the replacement of IKKα by IKKß in the IKK complex, although the detailed mechanism of this event remains to be elucidated. Reintroduction of IKKα or kinase-inactive IKKα induced terminal differentiation in $Ikk\alpha^{-/-}$ keratinocytes, but reintroduction of IKKß, p65 (a major NF-κB protein), or IκBα did not (Hu et al., 2001). Furthermore, transgenic IKKα or kinase-inactive IKKα driven by the K14 promoter rescued the skin phenotypes of $Ikk\alpha^{-/-}$ mice (Sil et al., 2004). Also, normal skin development was observed in IKKα kinase-inactive knock-in ($Ikk\alpha^{AA/AA}$) mice with mutations at 178 and

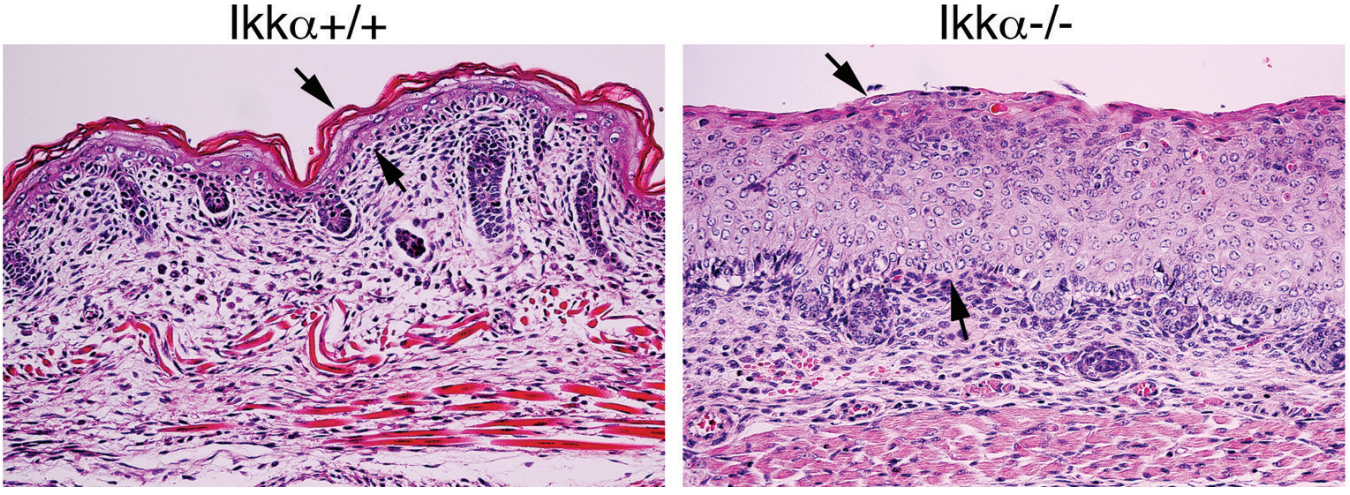

Fig. 1. IKKα loss induces epidermal hyperplasia, prevents terminal differentiation, and impairs the formation of the skin. Two arrows indicate the epidermis of the skin. The hematoxylin and eosin-stained paraffin sections were obtained from newborn mice with an FVB background. Original magnifications, x 200

180 (serine/alanine) within the ATP activation loop, and in *Ikkα*$^{K44A/K44A}$ mice with a mutation at the ATP binding site of the KD (Cao et al., 2001; Zhu et al., 2007). Taken together, these results clearly demonstrate that IKKα kinase activity is not required for the development of the mouse embryonic skin.

To date, the genetic pathways that lead to the skin phenotypes of *Ikkα*$^{-/-}$ mice remain largely unknown. Interestingly, repeated-epilation (Er) mice and interferon regulatory factor 6 (IRF6) knockout (I*rf6*$^{-/-}$) mice are similar in appearance to *Ikkα*$^{-/-}$ mice but express the normal levels of IKKα proteins (Herron et al., 2005; Ingraham et al., 2006; Li et al., 2005). This suggests that if Er and IRF6 were genetically connected, they would be downstream targets of IKKα during the mouse embryonic development. *Irf6* mutations were found in human Van der Woude syndrome and Nonsyndromic Cleft Lip with or without cleft palate (Item et al., 2004; Scapoli et al., 2005). *Ikkα*$^{-/-}$ mice have defects in facial and mouth development similar to those in *Irf6*$^{-/-}$ mice (Hu et al., 1999; Sil et al., 2004). Whether IKKα is involved in these human diseases remains to be shown. A mutation at the C-terminal region of the 14-3-3σ gene generates a truncated 14-3-3σ protein and has been found in Er mice (Herron et al., 2005). The 14-3-3σ gene, which functions as a G2/M cell cycle checkpoint, is highly expressed in keratinocytes and epithelial cells (Dellambra et al., 2000). It contains a 30-CpG cluster that is frequently hypermethylated, thus silencing 14-3-3σ in various human cancer cells (Ferguson et al., 2000; Gasco et al., 2002). Interestingly, we found that IKKα regulated 14-3-3σ expression at its transcriptional level by preventing DNA hypermethylation in keratinocytes (Zhu et al., 2007). Chromatin consists of DNA wound around nucleosome cores formed from histones. Trimethylation on lysine 9 of histone H3 (H3-K9) has been shown to be associated with DNA methylation, and consequently, transcriptional repression (Jackson et al., 2002; Fischle et al., 2003; Lehnertz et al., 2003; Tamaru et al., 2003). Further mechanistic study revealed that IKKα interacts with histone H3 in nucleosomes. By binding to H3, IKKα likely blocks the access of histone methyltransferase SUV39h1 to H3 (Rice et al., 2003; Stewart et al., 2005), thereby allowing 14-3-3σ transcription. However, whether IKKα and 14-3-3σ are in the same genetic pathway during mouse embryonic development remains to be shown. In addition, p63 has been reported to regulate IKKα expression in the formation of the epidermis (Candi et al., 2006; Koster et al., 2007). How p63 and IKKα cooperate to regulate the embryonic development also remains to be further investigated.

Human *Ikkα* gene and its association with human squamous cell carcinomas

The human *Ikkα* locus is located on chromosome 10 (10q24.31) (Mock et al., 1995). It has been reported that multiple tumor suppressors may be located on human chromosome 10q22-10q26 (Petersen et al., 1998). *Pten*, located at 10q23, is one such gene. In mice, *Ikkα* and *Pten* are located on chromosome 19. Liu et al. (2006) examined IKKα expression in 115 human cutaneous squamous cell carcinomas (SCCs) with different grades.

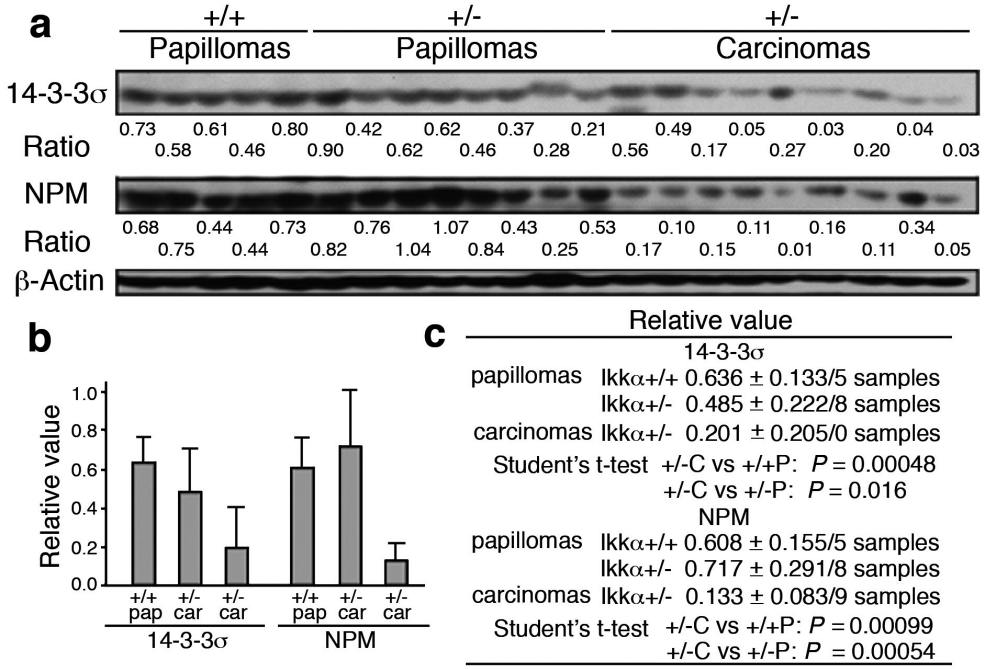

Fig. 2. Reduction of 14-3-3σ and NPM protein levels in skin carcinomas. **a.** 14-3-3σ and NPM levels in papillomas and carcinomas, detected by Western blotting. +/+ and +/-, *Ikkα*$^{+/-}$ and *Ikkα*$^{+/+}$; ß-Actin, a protein loading control; Ratio, densities of the IKKα signal normalized to those of the ß-Actin signal (ratio for wild-type skin was set as 1). Signals were scanned by a Kodak Image Station 440 with the ID3.6 software program (Kodak) and analyzed by the ImageQuant TL software program (version 2003.02). **b and c.** Comparison of relative 14-3-3σ and NPM levels in papillomas (pap) and carcinomas (car).

Immunohistochemical staining revealed that 14 (22.2%) of 63 grade I SCCs, 1 (2.3%) of 43 grade II SCCs, and none of the 9 grade III SCCs showed strong positive staining for the anti-IKKα antibody. Most of the grade II and III SCCs showed only weak positive staining for the anti-IKKα antibody. These results suggest that SCC aggressiveness is inversely correlated with the levels of IKKα expression in SCCs. In addition, Liu et al. (2006) found somatic mutations in exon 15 of *Ikkα* in human SCCs. Such mutations are believed to cause amino acid substitutions or nonsense mutations, or to generate stop codons, which might contribute to reduced expression, truncation, or destabilization of IKKα proteins.

Meada and colleague found that the expression of IKKα in human oral carcinoma cell lines was reduced (Maeda et al., 2007). Moreover, they detected no immunoreactivity of IKKα in 13 (33%) of 64 human oral SCCs and only weak IKKα immunoreactivity in 8 (12.5%) of 64 SCCs. The immunoreactivity was generally retained in well-differentiated carcinomas, but decreased in less-differentiated carcinomas and poorly differentiated carcinomas. Maeda et al. (2007) also reported that metastatic status and poor tumor differentiation were significantly correlated with poor patient survival rates. Thus, IKKα expression levels were statistically significantly associated with patient survival rates. Genetic instability of the IKKα gene was found in 29 (63%) of 46 oral SCCs by using microsatellite PCR. Loss of heterozygosity (LOH) of Ikkα was found in 2 oral SCCs. In addition, hypermethylation of CpG islands in the IKKα promoter (-253 to +66 base pair [bp]) was found in the human oral SCCs with reduced IKKα expression. Collectively, these results suggest that IKKα loss is associated with dedifferentiation, invasion, and progression of human oral SCCs.

In another recent study, A. Costanzo and M. Karin also detected loss or decreased expression of IKKα and nuclear IKKα in skin, lungs, and head and neck of human SCCs (Van Waes et al., 2007). Thus, IKKα is a tumor suppressor for human SCCs.

Role of IKKα in skin carcinogenesis in mice

The chemical carcinogen 7,12-dimethylbenz[a]anthracene (DMBA) causes activating H-Ras mutations in keratinocytes, and the tumor promoter 12-O-tetradecanoylphorbol-13-acetate (TPA) expands the Ras-initiated cell population in skin carcinogenesis in mice (Balmain and Pragnell, 1983). Studies have shown that in mice with a C57BL6 or a C56BL/129/Sv background, most papillomas eventually regress, but a few progress to form carcinomas that resemble human SCC (Hennings et al., 1993; Kemp et al., 1993). Mice with an FVB background have been found to be more susceptible to chemical skin carcinogenesis than mice with a C57BL6 background (Hennings et al., 1993). Using a two-stage chemical skin carcinogenesis protocol, we evaluated the susceptibility of IKKα to skin carcinogenesis in IKKα transgenic mice and in *Ikkα*$^{+/-}$ mice.

Gain of function of IKKα in skin carcinogenesis

IKKα expression in the skin has been reported to be elevated after TPA treatment (Saleem et al., 2004). However, the impact of elevated IKKα on skin carcinogenesis was previously not clear. Two studies have shown that K14.IKKα mice overexpressing IKKα in the basal epidermal keratinocytes driven by a K14 promoter and Lori.IKKα mice overexpressing IKKα in the basal and suprabasal keratinocytes driven by a truncated loricrin promoter develop normal skin (Sil et al., 2004; Liu et al., 2006). These results indicate that when IKKα is overexpressed in keratinocytes, normal embryonic skin development and skin function in adult mice are retained.

Lori.IKKα mice with an FVB background were further tested in a chemical carcinogen-induced skin carcinogenesis protocol (Liu et al., 2006). Although we found slightly fewer skin tumors in Lori.IKKα mice than in WT mice, we found significant fewer carcinomas and metastases in Lori.IKKα mice than in WT mice. Interestingly, IKKα protein levels were substantially reduced in poorly differentiated skin carcinomas derived from WT mice; however, no reduction in IKKα expression was detected in carcinomas derived from Lori.IKKα transgenic mice, although truncated IKKα proteins were observed in the carcinomas from Lori.IKKα mice, underscoring the importance of IKKα proteins in tumor progression (Liu et al., 2006). Because carcinomas derived from WT mice had a greater tendency to metastasize to lungs and lymph nodes than carcinomas from Lori.IKKα transgenic mice, it is possible that loss of the endogenous IKKα promotes the development of metastases. In addition, the presence of Ki67-positive keratinocytes and CD31-stained blood microvessels in the stroma was significantly higher in the skin of WT mice treated with DMBA/TPA than in the skin of Lori.IKKα mice treated with DMBA/TPA (Liu et al., 2006). Furthermore, ERK activities and vascular endothelial growth factor A (VEGF-A) levels were higher in the treated WT skin than in the treated Lori.IKKα skin. Taken together, these results suggest that elevated IKKα represses ERK activity and VEGF-A expression in the skin. Also, Ras has been shown to upregulate VEGF-A expression in keratinocytes (Larcher et al., 2003). Recently, IKKα was found to repress Ras-induced VEGF-A expression and was found to be associated with the distal promoter of VEGF-A by chromatin immunoprecipitation (ChIP) analyses. Furthermore, RasV61 attenuated IKKα binding to the VEGF-A promoter, which led to upregulation of VEGF-A expression in keratinocytes (Liu et al., 2006). Thus, IKKα may inhibit Ras-induced tumor development by repressing angiogenic and mitogenic activities.

Loss of function of IKKα in skin carcinogenesis

Because *Ikkα*$^{-/-}$ mice die soon after birth (Hu et al.,

1999), the susceptibility of IKKα to chemical carcinogen-induced skin carcinogenesis was examined in *Ikkα*$^{+/-}$ mice with a C57BL6 background (Park et al., 2007). *Ikkα*$^{+/-}$ mice developed 2 times more papillomas and 11 times more malignant carcinomas resembling human SCCs than did *Ikkα*$^{+/+}$ mice. The tumor latency was shorter and the tumor size was significantly larger in *Ikkα*$^{+/-}$ than in *Ikkα*$^{+/+}$ mice. All tumors obtained from *Ikkα*$^{+/-}$ and *Ikkα*$^{+/+}$ mice contained chemical carcinogen-induced Ras mutations. Thus, a reduction in IKKα expression provided a selective growth advantage, which cooperated with Ras activity to promote the development of the skin tumors.

Notably, most of the *Ikkα*$^{+/-}$ carcinomas expressed little IKKα and approximately half of the *Ikkα*$^{+/+}$ papillomas expressed reduced IKKα protein levels. LOH of *Ikkα* was found in the *Ikkα*$^{+/-}$ carcinomas and in the *Ikkα*$^{+/-}$ papillomas with reduced IKKα proteins. These results suggest that IKKα loss promoted malignant conversion. IKKα levels were also dramatically reduced in poorly differentiated WT carcinomas. Somatic *Ikkα* mutations were found in IKKα transcripts of *Ikkα*$^{+/-}$ and *Ikkα*$^{+/+}$ carcinomas and papillomas. More *Ikkα* mutations were detected in carcinomas than in papillomas (Park et al., 2007). Thus, this provides evidence that genetic events are involved in IKKα downregulation, which promotes skin carcinogenesis.

Further functional analyses shed light on the potential mechanisms of how reduced IKKα expression promotes chemical carcinogen-induced skin carcinogenesis (Park et al., 2007). The number of BrdU stained positive cells, ERK activity, and expression of multiple growth factors and cytokines, including epidermal growth factor (EGF), heparin-binding (HB)-EGF, transforming growth factor α (TGFα), fibroblastic growth factor 2 (FGF2), FGF13, VEGF-A, TNFα, and IL-1 were higher in TPA-treated *Ikkα*$^{+/-}$ skins than in TPA-treated *Ikkα*$^{+/+}$ skins; similar results were observed in primary cultured *Ikkα*$^{+/-}$ and *Ikkα*$^{+/+}$ keratinocytes (Park et al., 2007). Thus, the elevated mitogenic activities in *Ikkα*$^{+/-}$ skin were keratinocyte autonomous. In addition, ERK and IKK activities were higher in carcinomas than in papillomas, and levels of IκBα proteins were lower in carcinomas than in papillomas. Interestingly, IKK activities were higher in *Ikkα*$^{+/-}$ carcinomas than in *Ikkα*$^{+/+}$ carcinomas but IKKß levels were not significantly different among such papillomas and carcinomas. A previous study showed that IKK and NF-κB DNA binding activities were substantially elevated in *Ikkα*$^{-/-}$ keratinocytes after TNFα and IL-1 stimulation compared with those in *Ikkα*$^{+/+}$ keratinocytes; this result was thought to be caused by the replacement of IKKα by IKKß in the IKK complex (Hu et al., 2001). Thus, IKKα loss may contribute to the enhancement of IKK activities in poorly differentiated carcinomas, although additional mechanisms involved in this event remain to be revealed (Park et al., 2007). Collectively, excessive ERK, IKK, and NF-κB activities, and elevated expression of multiple growth factors and cytokines might provide molecular bases to promote Ras-initiated skin tumor formation and malignant conversion.

The tumor suppressor gene *Pten* is close to the *Ikkα* gene in human and mouse chromosomes. Somatic mutations in the *Pten* gene have been reported in many human cancers (Bonneau and Longy, 2000). *Pten*$^{+/-}$ mice developed more skin tumors than did *Pten*$^{+/+}$ mice in a two-stage chemical carcinogen-induced skin carcinogenesis setting (Mao et al., 2004). LOH of *Pten* and elevated AKT activities were detected in *Pten*$^{+/-}$ carcinomas, but, neither Ras mutations nor elevated ERK activities were detected in the *Pten*$^{+/-}$ carcinomas. Furthermore, no Pten mutations or reduction in Pten expression were detected in carcinomas derived from *Pten*$^{+/+}$ mice. Taken together, these data suggest that IKKα, unlike Pten, is a natural target of chemical carcinogen-induced skin carcinogenesis.

SCC cells showed mixed morphologies, with some cells having a more differentiated morphology and some having a less differentiated morphology (Park et al., 2007). The cells of poorly differentiated SCCs are usually quite uniformed. We found that the cells in *Ikkα*$^{+/-}$ carcinomas that lost wild-type IKKα allele were more uniformed than the cells in *Ikkα*$^{+/+}$ carcinomas. We isolated several IKKα cDNAs from WT DMBA/TPA-induced skin carcinomas and found that they contained various mutations. We found that the IKKα cDNAs with several *Ikkα* mutations lost their ability to induce terminal differentiation in *Ikkα*$^{-/-}$ keratinocytes, whereas those with fewer *Ikkα* mutations only had a reduction in their ability to induce terminal differentiation in *Ikkα*$^{-/-}$ keratinocytes (Zhu et al., 2007). Because *Ikkα* mutations were frequently detected in the chemical carcinogen-induced skin carcinomas, it is likely that they affect the status of cell differentiation and cell morphologies in those skin carcinomas.

IKKα loss has been found to downregulate the G2/M cell cycle by silencing the 14-3-3σ gene, which is a G2/M cell cycle checkpoint, in keratinocytes (Zhu et al., 2007). Reintroduction of IKKα or 14-3-3σ rescued the defect of G2/M cell cycle checkpoint in response to DNA damage. Thus, IKKα carries out its function in the regulation of the cell cycle checkpoint through 14-3-3σ. Aged Er mice with mutant 14-3-3σ were found to develop spontaneous skin carcinomas (Herron et al., 2005). Levels of 14-3-3σ have been shown to be reduced in chemical carcinogen-induced skin carcinomas that expressed little IKKα but not in papillomas (Fig. 2a-c) (Park et al., 2007). Thus, a reduction in 14-3-3σ expression is a possible mechanism involved in the enhancement of malignant conversion when IKKα is impaired during skin carcinogenesis in mice. In addition, a high number of aneuploid chromosomes have been reported in late-stage chemical carcinogen-induced papillomas and carcinomas (Aldaz et al., 1988). Nucleophosmin (NPM) is a multi-functional protein that regulates centrosome duplication (Okuda et al., 2000). Also, loss of NPM has been reported to cause unrestricted centrosome duplication, which affects chromosome segregation, leading to genomic instability

in cells (Grisendi et al., 2005). *Npm*$^{-/-}$ mice are embryonic lethal and *Npm*$^{+/-}$ mice have accelerated oncogenesis induced by c-myc. We found that NPM expression was dramatically reduced in skin carcinomas, but not in papillomas (Fig. 2a-c). These alterations in NPM expression might also be important for malignant conversion during skin carcinogenesis although a direct connection between IKKα and NPM remains to be revealed. Collectively, these results suggest that IKKα loss may promote malignant conversion through multiple targets.

Conclusion

In summary, IKKα is required for the development of the embryonic skin and has been shown to suppress skin carcinogenesis. Impaired IKKα expression has been shown to be associated with human cancers. This highlights the importance of IKKα in the prevention of cancers. Therefore, more mechanistic studies on IKKα functions will help us to identify therapeutic targets for battling against human cancers.

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