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Regulation of Apoptosis during Environmental Skin Tumor Initiation

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Abstract

Skin cancer is more prevalent than any other cancer in the United States. Non-melanoma skin cancers are the more common forms of skin cancer that affect individuals. The development of squamous cell carcinoma, the second most common type of skin cancer, can be stimulated by exposure of environmental carcinogens, such as chemical toxicants or UVB. It is developed by three distinct stages: initiation, promotion, and progression. During the initiation, the fate of DNA-damaged skin cells is determined by the homeostatic regulation of pro-apoptotic and anti-apoptotic signaling pathways. The imbalance or disruption of either signaling will lead to the survival of initiated cells, resulting in the development of skin cancer. In this chapter, we will discuss signaling pathways that regulate apoptosis and the impact of their dysfunction during skin tumor initiation.

Keywords: apoptosis, tumor initiation, skin, carcinogen, UVB, AKT, STAT3, MAPK, TC-PTP

1. Introduction

Apoptosis, also called programmed cell death, is an essential cellular process that is required to maintain tissue homeostasis by modulating various biological functions including embryonic development, cellular growth, and immunity through the elimination of unwanted cells. Apoptosis accompanies the distinct morphological changes, such as membrane blebbing, cell shrinkage, chromatin condensation, and DNA fragmentation. These morphological changes during apoptosis were first observed by John Foxton R. Kerr, Andrew H. Wyllie, and Alastair Currie in 1972 with the first description of “apoptosis” [1]. Later, the critical role of programmed cell death occurred during the development of the nematode *Caenorhabditis elegans* was elucidated with the finding of death-related genes in 1999 [2]. Three scientists – Sydney Brenner, H. Robert Horvitz, and John E. Sulston – were awarded the Nobel Prize in Physiology or Medicine in 2002 for their discovery of genes that regulate apoptosis. Since then, apoptosis has extensively been studied as a crucial biochemical mechanism for the maintenance of normal tissue function and homeostasis. Dysregulation of apoptosis has been involved in various types of human diseases including cancers and neurodegenerative diseases [3, 4].

Cells can die prematurely by injury, infection, external assault such as chemicals, or a lack of blood supply through energy-independent process of cell death, which is called by necrosis. Necrosis is an unplanned cellular death by external damage. It causes severe disorganization and rupture of subcellular structure and eventually leads to disruption of the cell membrane. Then, the exposure of cellular components of necrotic cells into the surrounding interstitial tissue results in inflammation. In contrast to necrosis, apoptotic cell death is highly ordered and energy-dependent molecular process that can eliminate unwanted and damaged cells without causing inflammation [5, 6].

Apoptosis is initiated by two different pathways: the extrinsic and the intrinsic pathways. The extrinsic pathway is mediated by the interaction of transmembrane receptors known as death receptors with their ligands. Death receptors are members of the tumor necrosis factor (TNF) gene family and share similar cysteine-rich extracellular domains and homologous intracellular cytoplasmic sequence named as the 'death domain'. The death domain of receptors transmits the death signal from the cell surface to the intracellular signaling pathways to induce apoptosis in a rapid and efficient manner. For example, the binding of Fas ligand with Fas receptor, TNF α with TNF receptor, and TNF-related apoptosis-inducing ligand (TRAIL) with TRAIL receptor 1, 2 results in the interaction of the death domain of receptor with the adaptor protein, such as Fas-associated death domain (FADD) or TNF receptor-associated death domain (TRADD). The adaptor protein then associates with procaspase-8 and converts it into active caspase-8 [3, 7]. Likewise, the intrinsic pathway, which is known as the mitochondrial pathway, is activated by a broad range of exogenous and endogenous stimuli including radiation, toxins, viral infections, and oxidative stress. It modulates mitochondrial membrane potential through change of the ratio of pro-apoptotic and anti-apoptotic proteins located in the mitochondria and releases cytochrome c from the intermembrane space into the cytoplasm. Cytochrome c then forms a multi-protein complex called as the 'apoptosome' with apoptotic protease activating factor 1 (APAF1) and recruits inactive procaspase-9, which is followed by the dimerization and generation of catalytically active caspase-9 in an ATP-dependent manner [8, 9]. Initiation of both the extrinsic and intrinsic pathways can lead to the activation of executioner caspases, such as caspase-3, 6, or 7, resulting in the morphological changes of apoptosis [10]. These two apoptotic pathways are interconnected. The cleavage of pro-apoptotic protein Bid by caspase-8 can lead to its translocation to the mitochondria and result in the activation of the mitochondrial pathway [11]. Environment toxicants, such as ultraviolet B (UVB) radiation and chemical carcinogens, can cause severe DNA damage, which activates the intrinsic pathway in skin [12, 13]. UVB radiation can also activate the extrinsic pathway by inducing Fas receptor by p53 activation, promoting the association of TNF receptor 1 with TNF receptor-associated factor-2 (TRAF-2), or inhibiting the interaction of TRAIL receptors with decoy receptors that serve as their negative binding partners for apoptosis (**Figure 1**) [14–17].

In intrinsic pathway, mitochondrial outer membrane permeability is regulated by pro-apoptotic or anti-apoptotic proteins of B-cell lymphoma 2 (Bcl-2) family. A total of 25 genes in the Bcl-2 family have been identified. The pro-apoptotic proteins of Bcl-2 family include Bax, Bak, Bid, Bim, Bad, Noxa, Bmf, and Puma. The anti-apoptotic proteins of Bcl-2 family include Bcl-2, Bcl-X_L, Bcl-w, Mcl-1, and BAG. Altered expression of Bcl-2 family proteins has been involved in various diseases including cancer [18–21].

Skin, the largest organ of the human body, is continuously exposed to environmental assaults. Exposure of skin to the chemical carcinogens or UVB radiation induces a mutation in critical gene or genes and forms specific carcinogen-DNA adducts. These adducts can be repaired by DNA repair mechanism. Otherwise, they need to be removed by apoptosis. Defected apoptosis by genetic abnormalities and

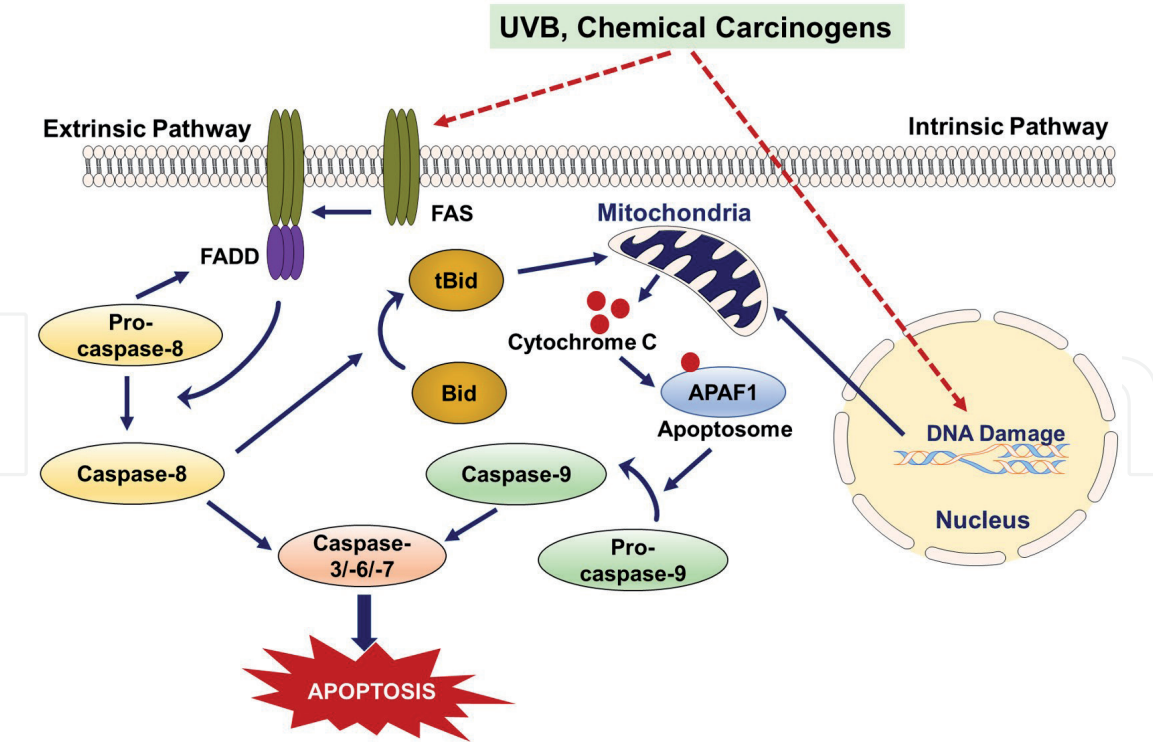


Figure 1.
Mechanisms of apoptosis induced by environmental carcinogens in skin. Apoptosis is initiated by two major pathways: The extrinsic and the intrinsic pathways. The extrinsic pathway is mediated by death receptors, such as Fas receptor. Upon binding to Fas ligand, Fas receptor interacts with FADD and recruits procaspase-8, which is followed by activation of caspase-8. The intrinsic pathway causes DNA damage and modulates mitochondrial membrane potential. Then, cytochrome c is released from the mitochondria into the cytoplasm. The formation of apoptosome with cytochrome c and APAF1 recruits and activates caspase-9. Activation of either caspase-8 or caspase-9 leads to the activation of executioner caspases including caspase-3, resulting in the morphological changes of apoptosis. These two pathways are also interconnected. The cleavage of bid by caspase-8 leads to its translocation to the mitochondria and activates the mitochondrial pathway. Environment toxicants, such as UVB radiation and chemical carcinogens, cause severe DNA damage and activate the intrinsic pathway in skin. UVB radiation activates the extrinsic pathway by activating death receptors and enhancing the association of death receptors with their ligands.

subsequent imbalanced signaling pathways can cause the survival of damaged cells during the tumor initiation. These damaged cells can undergo clonal expansion during the tumor promotion and eventually develop skin cancer [22–25]. In this chapter, we will review anti-apoptotic signaling pathways – AKT, STAT3, and MAPK – and pro-apoptotic signaling pathway – protein tyrosine phosphatases (PTPs) –, which are involved in the regulation of apoptosis during skin tumor initiation.

2. Anti-apoptotic signaling in skin tumor initiation

2.1 AKT signaling

AKT (protein kinase B) is the human homolog of the viral oncogene *v-akt* and is associated with protein kinases A (PKA) and C (PKC) in humans [26, 27]. The three known AKT isoforms are derived from distinct genes (AKT1/PKB α , AKT2/PKB β and AKT3/PKB γ). The N terminus of AKT contains a pleckstrin homology domain, which can mediate lipid-protein and/or protein–protein interactions [28–30]. The C terminus of AKT contains a hydrophobic and proline-rich domain [28, 29]. AKT is activated by various growth factors such as platelet-derived and fibroblast growth factors and is involved in the regulation of cell survival signaling [31, 32]. AKT activation depends on its phosphorylation and four different phosphorylation sites on AKT (Ser-124, Thr-308, Thr-450, and Ser-473) have been identified [33]. Studies

showed that extracellular stimuli induce the phosphorylation of AKT at Thr-308 and Ser-473 residues while the phosphorylation of AKT at Ser-124 and Thr-450 residues appears to be basally maintained [33]. Mutagenesis studies have revealed that the phosphorylation of AKT at Thr-308 and Ser-473 is required for its activation [34].

It has been shown that AKT signaling inactivates several pro-apoptotic factors including BAD, procaspase-9 and Forkhead transcription factors [35, 36]. In contrast, AKT activates various transcription factors that are involved in the upregulation of anti-apoptotic genes, such as cyclic-AMP response element-binding protein (CREB). It also activates I κ B kinase (IKK) to phosphorylate I κ B (inhibitor of NF- κ B), leading to its proteasomal degradation and NF- κ B nuclear localization. In addition, AKT reduces the protein levels of p53 by promoting its degradation through MDM2 phosphorylation, which can contribute to centrosome hyperamplification and chromosome instability in cancer [37, 38]. Furthermore, AKT is involved in the regulation of subcellular localization of proteins. AKT can regulate the localization of various proteins and thereby their activity by phosphorylating specific binding sites for 14-3-3 proteins, which play a crucial role in the modulation of cellular location and degradation of proteins [39, 40].

Studies have shown that AKT is activated by environmental toxicants including UVB irradiation which protects keratinocytes against environmental attacks, implying its anti-apoptotic role in skin tumor initiation. It has been shown that UV radiation induces phosphorylation of AKT at Ser-473 and Thr-308 residues in mouse epidermal cell JB6 Cl41 in a time-dependent manner. These results were further confirmed by the observation that overexpression of AKT mutant, AKT-T308A/S473A, attenuated phosphorylation of AKT at Ser-473 and Thr-308 upon UVB irradiation [41]. The reactive oxygen species (ROS) generated by UV radiation acts as a mediator in UV-induced phosphorylation of AKT. It has been observed that pre-treatment of cells with either an antioxidant, N-acetyl-L-cysteine (NAC) or a specific antioxidant enzyme (catalase) inhibits phosphorylation of AKT in these cells, suggesting the link of ROS in UV radiation-induced activation of AKT [41]. Specific phosphorylation of Bad, a pro-apoptotic member of the Bcl-2 family, by AKT delayed the early activated apoptotic pathways in UVB-exposed human keratinocytes. AKT-mediated phosphorylation of Bad at serine 136 residue promoted its translocation from the mitochondria to the cytoplasm and subsequent cytoplasmic sequestration by 14-3-3 ζ , resulting in the reduction of UVB-induced apoptosis in keratinocytes [42]. In addition to its anti-apoptotic function, studies using transgenic mice have shown that AKT can contribute to the development of skin cancer formation induced by environmental exposure through the regulation of epidermal proliferation. It has been shown that mice lacking *Akt1*^{-/-}; *Akt2*^{-/-} or *Akt1*^{-/-}; *Akt3*^{+/-} exhibit a hypoplastic epidermis due to decreased proliferation of keratinocytes while overexpression of wild type AKT1 (*wtAkt*) or constitutively active AKT (*myrAkt*) in the basal layer of mouse epidermis displays alterations in epidermal proliferation and differentiation [43–45]. Overexpression of either wtAKT or myrAKT in mouse epidermis displayed enhanced sensitivity to two stage skin carcinogenesis by promoting cell proliferation [45]. These studies suggest that AKT plays a critical role in the regulation of apoptosis and proliferation during skin carcinogenesis. Further detailed studies using transgenic mouse models will be helpful to elucidate the underlying molecular mechanisms and function of AKT in the initiation of skin carcinogenesis.

2.2 STAT3 signaling

Signal transducer and activator of transcription 3 (STAT3) is one of the family members of seven [STAT1 (α and β splice isoforms), STAT2 and STAT3 (α and β

isoforms), STAT4, STAT5a, STAT5b, and STAT6)] latent cytoplasmic transcription factors which are encoded by seven individual genes [46]. STATs are phosphorylated at their specific tyrosine residue and activated by a wide variety of stimuli including growth factors and cytokines, which act through intrinsic receptor tyrosine kinases [47]. Tyrosine phosphorylation of STAT induces its dimerization via reciprocal interaction of phospho-tyrosine with Src homology domain 2 (SH2) between two STAT molecules. The phosphorylated STATs then translocate to the nucleus and bind to the consensus promoter sequences of downstream target genes, resulting in the activation of their transcription [48].

Different tyrosine kinases, such as RTKs (receptor tyrosine kinases) and non-RTKs including JAKs (Janus kinases), can phosphorylate STAT proteins. STAT tyrosine phosphorylation is transient, which lasts from 30 minutes to several hours in normal cells. However, studies have shown that STATs (specifically STAT3) are persistently tyrosine phosphorylated either as a consequence of deregulation of positive regulators of STAT activation such as tyrosine kinases or deactivation of negative regulators of STAT phosphorylation, such as phosphatases, suppressor of cytokine signaling, or protein inhibitor of activated STATs, in numerous cancer-derived cell lines or in primary tumors [49].

Studies have revealed that STAT3 is associated with cell survival and oncogenic transformation among the seven members of STATs. It has shown that targeted inhibition of STAT3 activation by antisense, small interfering RNA, dominant-negative STAT3 constructs, and/or blockade of tyrosine kinases has been associated with growth arrest and induction of apoptosis in cancer cell lines [49]. Furthermore, overexpression of constitutively activated STAT3 into immortalized cell lines led to oncogenic transformation, indicating a potential role of STAT3 in carcinogenesis [50, 51].

The generation of epidermal-specific STAT3-deficient and STAT3-overexpressing transgenic mice led to the main discovery of functional role of STAT3 in the initiation stage of skin carcinogenesis [52, 53]. Epidermal-specific deficiency of STAT3 in mouse (*K5Cre.Stat3^{fl/fl}*) significantly increased the sensitivity to apoptosis after 7,12-dimethylbenz[a]anthracene (DMBA) treatment both *in vitro* keratinocytes and *in vivo* epidermis compared with non-transgenic controls, as determined by increased caspase-3-positive cells. In particular, the significant increase in the number of keratinocyte stem cells (KSCs) undergoing apoptosis in the bulge region of hair follicles was observed in STAT3-deficient mice compared with non-transgenic littermates, indicating that STAT3 may be critical for maintaining the survival of KSCs during skin tumor initiation mediated by DMBA [54]. Similar with this observation, forced expression of a constitutively active form of STAT3 in mouse epidermis (*K5.Stat3C*) showed increased cell survival following DMBA exposure [55]. Further studies showed that STAT3 plays a critical role in the protection of damaged keratinocytes after UVB exposure. The epidermis of STAT3-deficient mice was highly sensitive to UVB-induced apoptosis compared with the epidermis of control mice, whereas the epidermis of *K5.Stat3C* mice was more resistant to UVB-induced apoptosis compared with the epidermis of control mice. UVB induces DNA damage and causes mutations in runs of tandemly located pyrimidine residues of DNA, resulting in the generation of cyclobutane pyrimidine dimers (CPDs) and pyrimidine (6–4) pyrimidone photoproducts (6–4 PPs). The number of either 6–4 PP- or CPD-positive cells was greater in epidermis of *K5.Stat3C* mice compared with epidermis from STAT3-deficient mice after UVB exposure [56]. Additionally, generation of inducible STAT3-deficient mice (*K5.Cre-ER^{T2} × Stat3^{fl/fl}*) clearly demonstrated that STAT3 has a critical role in the protection of keratinocytes during tumor initiation. Inducible deletion of STAT3 in mouse epidermis significantly increased apoptosis after DMBA treatment. Inducible STAT3 deletion in epidermis

before initiation with DMBA showed a significant delay in tumor development and a significantly reduced number of tumors compared with control groups in two-stage skin carcinogenesis [57].

Expression of *Ha-ras* homolog (*v-Ha-ras*) into cultured primary keratinocytes *in vitro* has been utilized to generate initiated keratinocytes. Studies showed that the introduction of a STAT3 decoy molecule into the *v-Ha-ras*-initiated keratinocytes increases apoptosis with a concomitant decrease in Bcl-xL expression levels. In general, inhibition of STAT3 activation can lead to increase apoptosis or growth arrest in cancer-derived cell lines containing high levels of phosphorylated STAT3. However, STAT3 inhibition was not relatively affected in cell lines containing low or no levels of detectable tyrosine phosphorylated STAT3. Therefore, how STAT3 can protect keratinocytes against DMBA-induced apoptosis remains to be unclear, because DMBA does not induce tyrosine phosphorylation of STAT3 in keratinocytes, nor is it likely that *v-Ha-ras*-containing keratinocytes contain abundant levels of phosphorylated STAT3 [58]. One possible explanation is that the low levels of phosphorylated STAT3 present in these keratinocytes are sufficient to drive transcription of anti-apoptotic genes such as *Bcl-xL*. Alternatively, it is also possible that non-phosphorylated STAT3 may play a role as a transcription factor as previously demonstrated for STAT1 [59]. There are a few notable examples where relatively low levels of phosphorylated STAT3 are sufficient to mediate protection from growth arrest or apoptosis [60, 61]. Therefore, determination of the relative levels of phosphorylated STAT3 required to impart a phenotype is likely to be cell-type specific and remains an important objective.

It suggests that KSCs, which are located mostly within the bulge region of the hair follicle, are the major target cells for two-stage carcinogenesis [62]. The label-retaining cells (LRCs) retain the label for a sustained period of time following continuous administration of nucleotide analogs such as bromodeoxyuridine (BrdU) or [³H] thymidine, indicating a very slow cycling frequency. Studies showed that hair follicle KSCs are identified within the LRCs [63, 64]. It has been observed that the STAT3-deficient keratinocytes undergoing apoptosis following DMBA exposure were located primarily within the bulge region of the hair follicle in an area adjacent to the LRC population. It indicates that the DMBA-sensitive cells may be KSCs, given their proximity to the LRCs. However, given the lack of overlap between the LRCs and the apoptotic cells, the cell type most sensitive to DMBA-induced apoptosis remains to be identified. Studies using inducible bulge-region KSC-specific STAT3-deficient mice (*K15.CrePR1 × Stat3^{fl/fl}* mice) have provided further evidence that STAT3 is required for survival of bulge-region KSCs during the initiation stage of skin carcinogenesis [65]. In these studies, the number of apoptotic KSCs in the bulge-region was significantly increased in *K15.CrePR1 × Stat3^{fl/fl}* mice by inducible deletion of STAT3 prior to tumor initiation with DMBA compared with control littermates. In addition, the frequency of *Ha-ras* codon 61 A182 → T mutations was decreased in *K15.CrePR1 × Stat3^{fl/fl}* mice compared to control mice [65]. Furthermore, the number of skin tumors that developed in a two-stage skin carcinogenesis protocol was dramatically reduced by targeted deletion of STAT3 in bulge region KSCs at the time of initiation [65]. Overall, these studies provide molecular basis of STAT3 involvement in the initiation of skin carcinogenesis.

2.3 MAPK signaling

Mitogen-activated protein kinases (MAPKs) are essential signaling components that are vital in converting extracellular stimuli into intracellular responses through transcriptional regulation of various regulatory genes. MAPK signaling is activated by sequential protein kinase cascades including three enzymes: a MAPK kinase

kinase (MAPKKK), a MAPK kinase (MAPKK) and a MAPK [66]. MAPK signaling pathways are involved in the regulation of a wide variety of cellular processes including cell proliferation, differentiation, development, stress responses and apoptosis. Therefore, MAPK signaling is considered as one of potential therapeutic targets for many signaling-related diseases including cancer and diabetes. Three structurally related but biochemically and functionally distinct MAPKs are identified and named as extracellular signal-regulated kinases (ERKs), c-Jun N terminal kinases (JNKs) and p38 MAPKs [67–70].

ERK was the first MAPK identified and contains two isoforms: ERK1 and ERK2. ERK plays a critical role in the signaling of a variety of extracellular stimuli, such as growth factors and phorbol esters. ERK signaling is involved in the regulation of cell cycle progression and cell proliferation as one of major checkpoint signaling pathways for cellular mitogenesis [66, 71]. JNK was initially identified as a regulator of transcription factor c-Jun and consisted of three isoforms: JNK1, JNK2, and JNK3. JNK is also known as a stress-activated protein kinase (SAPK) as it is stimulated by various intra- or extracellular stresses. JNK signaling is involved in many cellular processes including immune response, neuronal activity, and insulin signaling [70, 72]. Studies have also shown that JNK signaling is critical in the promotion of apoptosis in response to a variety of harmful external stimuli through p53 activation [73, 74]. p38 MAPK contains four isoforms: p38 α , p38 β , p38 δ , and p38 γ . p38 MAPK is another SAPK and is activated by stress related stimuli. Similar with JNK, p38 MAPK is also involved in many cellular processes including apoptosis, inflammation, migration, differentiation, and cell cycle checkpoints [68, 75, 76].

In skin keratinocytes, both ERK and JNK are activated by UVB irradiation and protect cells against UVB-induced apoptosis [77, 78]. JNK is significantly activated by UVB exposure and pretreatment of antioxidant N-acetylcysteine reduced its activation, implying UVB-induced oxidative stress plays an important role in the activation of JNK [77]. Furthermore, UVB-mediated generation of reactive oxygen species significantly increased the activation of both JNK and ERK in human keratinocytes. Activated JNK and ERK then induced the upregulation of Bcl-2 and adenovirus E1B 19-kDa interacting protein 3 (BNIP3) expression, which is known to protect keratinocytes from UVB-induced apoptosis through autophagy. Pretreatment with the antioxidant N-acetylcysteine, the JNK inhibitor SP600125, or the ERK inhibitor U0126 significantly reduced the expression of BNIP3 upon UVB exposure and decreased cell survival by inducing apoptosis [78]. p38 MAPK is also activated by UVB irradiation [79]. However, in contrast to JNK and ERK, p38 MAPK promotes epidermal apoptosis following UVB exposure in mouse skin. The epidermis of transgenic mice that express a dominant negative p38 α MAPK (p38DN) showed a significant reduction in UVB-induced apoptosis compared with the epidermis of control mice. The p38DN mice also showed a significant reduction of tumor number and growth compared to wild-type mice in UVB skin carcinogenesis assay [80]. Overall, it implies that JNK and ERK may protect damaged keratinocytes by reducing apoptosis during the initiation of skin carcinogenesis induced by environmental carcinogens, while p38 MAPK may contribute to remove damaged keratinocytes by promoting apoptosis in response to environmental exposure.

3. Pro-apoptotic signaling in skin tumor initiation

3.1 PTPs in skin

PTPs negatively regulate the rate and duration of phosphotyrosine signaling as an endogenous negative feedback mechanism of protein tyrosine kinases (PTKs)

[81–84]. PTPs were first identified in the late 1980s by Nicholas Tonks and colleagues 10 years after the discovery of PTKs [85]. Since then, 107 PTPs have been identified in the human genome by using the conserved catalytic domain of PTPs to search the human genome database [86, 87].

It has been shown that PTP expression is induced during proliferation and maturation of keratinocytes, however their expression levels remain unchanged within skin epidermis [88]. In contrast, microarray analysis has shown that expression of PTPs, such as PTP κ and PTP λ decreases in human melanoma tissue compared with its normal counterpart [89, 90]. Studies showed that acute ultraviolet (UV) exposure leads to the ligand-independent activation of PTKs [91, 92]. This result indicates that UV radiation may reduce PTP activation. With this regard, biochemical analysis showed that reactive oxygen species (such as H₂O₂) produced by UV irradiation caused the inactivation of PTPs through the oxidization of the cysteine residue located within the conserved active-site of the PTP catalytic domain [93–95]. Furthermore, studies performed by different groups have revealed that acute UV exposure can trigger PTP inactivation in keratinocytes [96, 97].

In contrast to previous findings of PTP inactivation observed in skin, studies revealed that three PTPs, T-cell protein tyrosine phosphatase (TC-PTP), Src homology region 2 domain-containing phosphatase 1 (SHP1), and SHP2, can cooperate in the dephosphorylation of STAT3 in response to UVB irradiation [98]. STAT3 was rapidly dephosphorylated in keratinocytes after UVB irradiation. Knockdown of TC-PTP, SHP1, or SHP2 using RNAi in keratinocytes before UVB exposure partially recovered the level of phosphorylated STAT3 at Tyr 705 (PY-STAT3) compared to control keratinocytes, indicating that these PTPs are responsible for the rapid STAT3 dephosphorylation observed following UVB exposure. Further studies revealed that knockdown of all three phosphatases, using RNAi, prevented the rapid dephosphorylation of STAT3 following UVB irradiation [98]. This result suggests that exposure to UVB triggers PTP activation, which attenuates STAT3 signaling by dephosphorylating PY-STAT3. It implies that this activation of PTP can contribute to increase UVB-induced apoptosis during tumor initiation by deactivating STAT3, one of major survival factors in skin.

3.2 TC-PTP/PTPN2 signaling

Among three PTPs involved in STAT3 dephosphorylation of keratinocytes after UVB exposure, further investigation revealed that TC-PTP is the major PTP involved in the regulation of STAT3 signaling in keratinocytes following UVB exposure. TC-PTP activity was steadily increased after treatment of low-dose of UVB (10 mJ/cm²), which can contribute to STAT3 dephosphorylation in mouse keratinocytes. Knockdown of TC-PTP in mouse 3PC keratinocytes significantly suppressed UVB-induced apoptosis with decreased caspase-3 activity compared to control keratinocytes [99].

TC-PTP was one of the first members of the PTP gene family to be identified. It is encoded by protein tyrosine phosphatase non-receptor type 2 (PTPN2). As one of 17 intracellular, non-receptor PTPs, TC-PTP is broadly expressed in most embryonic and adult tissues, but it is highly expressed in hematopoietic tissues [100, 101]. Two different forms of TC-PTP are generated by alternative splicing at the 3' end of the gene: TC45 (TC-PTPa) and TC48 (TC-PTPb). TC45 (45 kDa) is the major form of TC-PTP in most species, including humans and mice. TC45 is mainly localized in the nucleus with a bipartite nuclear localization signal (NLS) in its C-terminal domain, while TC48 (48 kDa) is localized to the endoplasmic reticulum with its hydrophobic C terminus. Studies have shown that almost all TC-PTP mRNA encodes TC45 in mouse tissue and TC48 mRNA is not detectable by Northern blot analysis [102–104].

Recent generation of epidermal-specific TC-PTP knockout (*K14Cre.Ptpn2^{fl/fl}*; TC-PTP KO) transgenic mice as *in vivo* models has provided an evidence that TC-PTP plays a crucial role in the promotion of epidermal apoptosis induced by environmental assaults [105, 106]. TC-PTP deficiency in mouse epidermis led to a desensitization to tumor initiator DMBA-induced apoptosis both *in vivo* epidermis and *in vitro* keratinocytes. The number of apoptotic cells, detected by active caspase-3 staining, within the epidermis of control (TC-PTP WT) mice was significantly increased compared to TC-PTP KO mouse epidermis following DMBA treatment. Profound morphological changes induced by apoptosis, such as cell ballooning and bleb formation, were found in TC-PTP WT keratinocytes compared to TC-PTP KO keratinocytes. Similarly, annexin V-positive cells and caspase-3 activity were significantly increased in TC-PTP WT keratinocytes compared to TC-PTP KO keratinocytes. Inhibition of STAT3 or AKT in TC-PTP KO keratinocytes significantly reversed the effects of TC-PTP deficiency on apoptosis by increasing cellular sensitivity and caspase-3 activity following DMBA treatment compared to control keratinocytes [105]. Further studies also showed that TC-PTP KO cells showed increased survival against UVB-induced apoptosis compared to control, which was concomitant with a UVB-mediated increase in the level of Flk-1 (fetal liver kinase-1, known as VEGFR2) phosphorylation. Immunoprecipitation of the TC-PTP substrate-trapping mutant TCPTP-D182A showed that TC-PTP directly interacts with Flk-1 to dephosphorylate it and their interaction was stimulated by UVB irradiation. Following UVB-mediated Flk-1 phosphorylation in the absence of TC-PTP, the level of phosphorylated JNK was significantly increased in TC-PTP KO cells compared to TC-PTP WT cells after UVB irradiation. Inhibition of Flk-1 or JNK by their specific inhibitors in TC-PTP KO cells reversed this effect and significantly increased UVB-induced apoptosis compared to untreated TC-PTP KO cells [106].

The nuclear form of TC-PTP (TC45) contains bipartite nuclear localization signals (NLSI and NLSII) in its C-terminus, and TC45 had been known to be primarily localized in the cell nucleus due to its NLS [103]. However, recent studies have showed that TC45 is mainly localized to the cytoplasm of keratinocytes. TC45 is translocated to the nucleus following UVB irradiation [98]. TC45 nuclear translocation increased its activity in the nucleus and resulted in an increase of UVB-induced apoptosis which corresponded to a decrease in nuclear phosphorylated STAT3. UVB irradiation activated AKT to trigger nuclear translocation of TC45 and the adaptor protein 14-3-3 σ . Furthermore, site-directed mutagenesis of putative 14-3-3 σ binding sites within TC45 revealed that a substitution at threonine 179 (TC45/T179A) effectively blocked UVB-induced nuclear translocation of exogenous TC45 due to the disruption of the direct binding between TC45 and 14-3-3 σ . Overexpression of TC45/T179A in keratinocytes resulted in decreased UVB-induced apoptosis, indicating that TC45 nuclear translocation is an important step to induce apoptosis against UVB-mediated damage [107].

Recent generation of epidermal-specific TC-PTP-overexpressing (*K5HA.Ptpn2*) mouse model further demonstrated that TC-PTP has a critical role for the induction of epidermal apoptosis against chemical carcinogen [108]. Overexpression of TC-PTP increased epidermal sensitivity to DMBA-induced apoptosis through the synergistic regulation of STAT1, STAT3, STAT5, and PI3K/AKT signaling. Inhibition of STAT1, STAT3, STAT5, or AKT reversed the effects of TC-PTP overexpression on epidermal apoptosis after DMBA treatment [108].

Overall, these studies suggest that TC-PTP plays a protective role against environmental carcinogens by increasing epidermal apoptosis through the regulation of AKT, STAT including STAT3, and Flk-1/JNK signaling pathways (Figure 2).

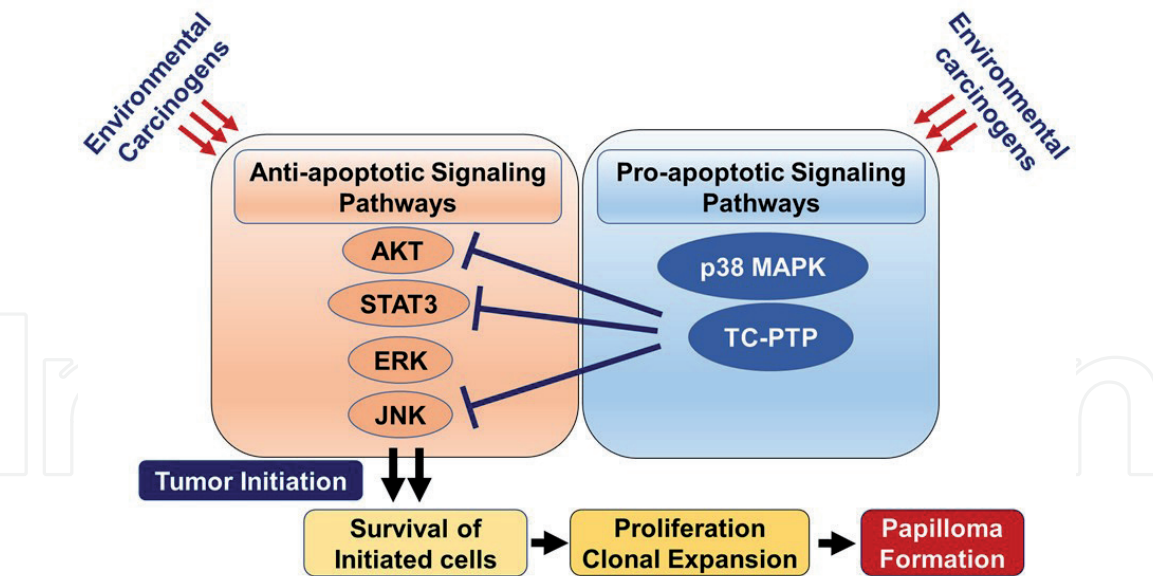


Figure 2. Anti-apoptotic and pro-apoptotic signaling pathways in the regulation of skin tumor initiation induced by environmental carcinogens. AKT, STAT3, ERK, and JNK signaling pathways inhibit epidermal apoptosis in response to environmental carcinogens, such as UVB and chemical carcinogens/toxins, which can lead to survival of DNA damaged cells during tumor initiation. These initiated cells are clonally expanded by accelerated proliferation during tumor promotion and form benign skin tumor called by ‘papilloma’. On the other hand, TC-PTP signaling pathway is initially activated against environmental exposure. TC-PTP signaling attenuates AKT, STAT3, and JNK signaling pathway through either direct or indirect dephosphorylation and increases epidermal apoptosis as one of initial protective mechanisms in skin. p38 MAPK signaling pathway is also activated and may contribute to increase epidermal apoptosis following environmental exposure.

4. Conclusion

Apoptosis is a critical cellular process to protect keratinocytes during skin tumor initiation. Environmental assaults induce a mutation in a critical gene or genes. Apoptosis can remove DNA-damaged keratinocytes that are not repaired via DNA damage repair mechanism. Survival of damaged keratinocytes by increased anti-apoptotic signaling pathways or decreased pro-apoptotic signaling pathways will lead to clonal expansion of them during skin tumor promotion, which is followed by the formation of papilloma and then squamous cell carcinoma. In this chapter, we outline the functional significance of three – AKT, STAT3, and MAPK – anti-apoptotic signaling pathways and TC-PTP as a pro-apoptotic signaling pathway in the regulation of apoptosis during skin tumor initiation. Besides them, different signaling pathways are involved in modulating apoptosis during skin tumor initiation depending on the types of environmental assaults and interconnected with signaling pathways we mentioned in this chapter. Further understanding of signaling mechanisms and their function in environmentally induced epidermal apoptosis during tumor initiation will contribute to develop novel therapeutic interventions for the prevention and treatment of skin cancer.

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Conflict of interest

No potential conflicts of interest were disclosed.

Competing financial interests

The authors declare no competing financial interests.

Appendices and nomenclature

6-4PP	pyrimidine (6–4) pyrimidone photoproduct
AKT	a serine/threonine specific protein kinase, known as protein kinase B (PKB)
APAF1	apoptotic protease activating factor 1
Bcl-2	B-cell lymphoma 2
BNIP3	Bcl-2 and adenovirus E1B 19-kDa interacting protein 3
Caspase	cysteine-aspartic protease, cysteine aspartase or cysteine-dependent aspartate-directed protease
CREB	cyclic-AMP response element-binding protein
CPD	cyclobutane pyrimidine dimer
DMBA	7,12-dimethylbenz[a]anthracene
ERK	extracellular signal-regulated kinase
FADD	Fas-associated death domain
Flk-1	fetal liver kinase-1, known as VEGFR2
JAK	Janus kinase
JNK	c-Jun N-terminal kinase
K5	keratin 5
K14	keratin 14
KO	knockout
KSC	keratinocyte stem cell
LRC	label-retaining cell
MAPK	mitogen-activated protein kinase
NLS	nuclear localization signal
p38DN	dominant negative p38 α MAPK
PTP	protein tyrosine phosphatase
PTK	protein tyrosine kinase
PTPN2	protein tyrosine phosphatase non-receptor type 2
PY-STAT3	phosphorylated STAT3 on the tyrosine residue
RNAi	RNA interference
RTK	receptor tyrosine kinase
SAPK	stress-activated protein kinase
SHP-1	Src homology region 2 domain-containing phosphatase-1
SHP-2	Src homology region 2 domain-containing phosphatase-2
STAT3	signal transducer and activator of transcription 3
TC-PTP	T-cell protein tyrosine phosphatase
TRADD	TNF receptor-associated death domain
TRAF-2	TNF receptor-associated factor-2
TRAIL	TNF-related apoptosis-inducing ligand
TNF	tumor necrosis factor
UVB	ultraviolet B
WT	wild type

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