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The role of T-cell protein tyrosine phosphatase in epithelial carcinogenesis

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Abstract

T-cell protein tyrosine phosphatase (TC-PTP, encoded by *PTPN2*) is a non-receptor PTP that is mostly highly expressed in hematopoietic tissues. TC-PTP modulates a variety of physiological functions including cell cycle progression, cell survival and proliferation, and hematopoiesis through tyrosine dephosphorylation of its target substrates, such as EGFR, JAK1, JAK3, STAT1, and STAT3. Studies with whole or tissue-specific loss of TC-PTP function transgenic mice have shown that TC-PTP has crucial roles in the regulation of the immune response, insulin signaling, and oncogenic signaling. More recently, generation of epidermal-specific TC-PTP-deficient mice for use in multistage skin carcinogenesis bioassays demonstrated that TC-PTP suppresses skin tumor formation by negatively regulating STAT3 and AKT signaling. Further investigation showed that TC-PTP also minimizes UVB-induced epidermal cell damage by promoting apoptosis through the negative regulation of Flk-1/JNK signaling. These findings provide major evidence for a tumor suppressive function for TC-PTP against environment-induced skin cancer. Here, we will discuss TC-PTP, its substrates, and its functions with an emphasis on its role in skin carcinogenesis.

Keywords

TC-PTP; carcinogenesis; STAT3; AKT; Flk-1

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INTRODUCTION

Phosphotyrosine-based signaling is one post-translational mechanism essential for eukaryotic inter- and intracellular communication regulating cell proliferation, differentiation, survival, and migration. The state of cellular tyrosine phosphorylation is well-regulated by the opposing activities of protein tyrosine kinases (PTKs) and protein tyrosine phosphatases (PTPs), which catalyze the addition or removal, respectively, of phosphate groups from specific tyrosine residues within proteins [1–6]. Genetic mutation of PTKs and/or aberrant activation of their signaling pathways can lead to any number of human diseases including cancer [7,8]. Consequently, PTKs have been a primary focus of cancer prevention research for many years. Given the natural ability of PTPs to regulate PTK activity, PTPs also became an attractive target for potential anticancer interventions.

PTPs were first identified in the late 1980s by Nicholas Tonks and colleagues, approximately 10 years after the discovery of PTKs [9]. Since then, studies using the conserved catalytic domain of PTPs to search the human genome database have identified at least 107 PTPs encoded in the genome [10,11]. PTPs are classified into four classes based on the amino acid sequences of their catalytic domains: class I (the tyrosine specific phosphatases), class II (the low molecular weight PTPs), class III (the dual specific cdc25 phosphatases), and class IV (the Eya-related aspartate-based PTPs). The largest class, the class I cysteine-based PTPs, consists of 99 PTPs that can be further subdivided into two groups: (i) the 38 well-known classical PTPs with strict specificity for phosphotyrosine and (ii) the VH-1 like dual specific phosphatases. The classical PTPs are categorized by subcellular localization as either receptor-like PTPs or non-receptor-like PTPs [12–15].

Functional studies demonstrated that PTPs are associated with carcinogenesis [13,16]. Of the 38 classical PTPs, 22 have been shown to play a tumor suppressive role in different types of human cancer [11]. On the other hand, other PTPs have been shown to act as oncogenes by stimulating cell proliferation and survival. Studies have identified 11 of the 38 classical PTPs act as potential oncogenes [11,17,18]. Environmental factors, such as UV light, are known to contribute to the development of skin cancer by stimulating PTK signaling, so studies on PTPs in skin have mainly focused on their role in PTK inactivation as a means of identifying the mechanism(s) that enhances PTK activation in cancer. For instance, it was shown that exposure to acute ultraviolet (UV) irradiation increases the ligand-independent activation of PTKs [13,14], implying that UV radiation inactivates PTPs. However, our recent studies have provided evidence that PTP-mediated signaling plays a critical role in a protective mechanism against skin carcinogenesis. Specifically, we have demonstrated that T-cell protein tyrosine phosphatase, or TC-PTP, is activated during the initial response to environmental assault to inhibit keratinocyte survival and proliferation which leads to the attenuation of squamous cell carcinoma. In this review, we will provide background on TC-PTP and its known substrates, and we will discuss the current knowledge on its various roles and functions in the context of cancer, with a specific emphasis on our recent findings elucidating the role(s) TC-PTP plays in the initiation and promotion of skin cancer.

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T-CELL PROTEIN TYROSINE PHOSPHATASE AND ITS TARGET SUBSTRATES

TC-PTP, also known as protein tyrosine phosphatase non-receptor type 2, is encoded by the *PTPN2* gene and it was one of the first members of the PTP gene family to be identified. TC-PTP is one of 17 intracellular, non-receptor PTPs. It is most highly expressed in hematopoietic tissues, but it is also ubiquitously expressed in embryonic and adult tissues [19–23]. TC-PTP is a non-transmembrane protein comprised of a conserved catalytic domain and a non-catalytic C-terminal domain. Alternative splicing at the 3' end of *PTPN2* generates two variants of TC-PTP: TC45 (45 kDa) and TC48 (48 kDa). TC45 is the major form of TC-PTP in most species including human and mouse. It possesses a shortened hydrophilic C-terminal domain with bipartite nuclear localization signals, known as NLSI and NLSII. Consequently, TC45 is found in the nucleus of most cell types, and it is translocated to the cytoplasm in response to growth factor and cytokine receptor signaling to dephosphorylate its substrates [21–23]. However, our recent studies have demonstrated TC45 localization is also dependent on cell type and state. Our findings showed TC45 was mainly localized within the cytoplasm of keratinocytes but it underwent nuclear translocation following stimulation by UVB radiation, thus facilitating an increase in TC45 activity in the nucleus. We found UVB irradiation triggered AKT kinase-mediated phosphorylation of TC45 at threonine residue 179 (T179) and this modification created a recognition motif for the direct binding of the adaptor protein 14–3-3σ to TC45 in order for 14–3-3σ to shuttle TC45 into the keratinocyte nucleus (Figure 1). TC45 nuclear translocation accelerated nuclear STAT3 (signal transducer and activator of transcription 3) dephosphorylation, resulting in decreased cell proliferation and increased apoptosis. Disruption of 14–3-3σ/TC45 binding at T179 or loss of NLSII blocked UVB-induced nuclear translocation, indicating both these sites are required for efficient nuclear translocation of TC45 upon UVB irradiation [24,25]. Interestingly, Simoncic et al. reported TC-PTP was localized in the cytoplasm of hematopoietic cells as well [26]. TC48, on the other hand, contains a hydrophobic C-terminus and is localized to the endoplasmic reticulum (ER). Our research showed UVB irradiation had no effect on TC48 localization in keratinocytes [24].

TC-PTP has several substrates: EGF (epidermal growth factor) receptor, adaptor protein $p52^{Shc}$, insulin receptor (IR), JAK (Janus kinase) 1, JAK3, STAT1, and STAT3 [26–33]. Using a substrate-trapping recombinant TC45 protein, Tiganis et al. demonstrated that phosphorylated EGFR directly bound to TC48 in the ER of COS-1 cells. Furthermore, phosphorylated EGFR and $p52^{Shc}$ also formed complexes with TC45 following EGF-induced translocation of TC45 from the nucleus to the cytoplasm of COS-1 cells [27]. Interaction of TC45 with EGFR allowed it to function as a negative regulator of growth factor or integrin-induced, EGFR-mediated phosphatidylinositol 3-kinase (PI3K) signaling by preventing the recruitment of the p85 regulatory subunit of PI 3-kinase by EGFR [28]. PI3K signaling is a major mechanism involved in a number of cellular processes such as cell growth, proliferation, differentiation, survival and intracellular trafficking [34,35]. For instance, PI3K signaling can function as a part of insulin signaling. Substrate-trapping mutants were utilized to demonstrate IR is a substrate of TC-PTP, indicating TC-PTP can

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down-regulate insulin signaling at the initial step [32,36]. Investigation by Galic et al. additionally revealed stimulation of HEK293 cells with insulin induced binding of both TC45 and TC48 with the β-subunit of active IR [32].

Simoncic et al. identified JAK1 and JAK3 as direct substrates of TC-PTP. In their studies, cytotoxic T cells (CTLL-2) expressing a TC-PTP substrate-trapping mutant were stimulated with IL-2 which induced binding of TC-PTP to JAK1 and JAK3, and treatment with IFN-γ of HEK 293T cells expressing the TC-PTP substrate-trapping mutant also triggered TC-PTP/JAK1 complex formation [26]. Cytokine signaling is critical for complex immunological processes such as lymphocyte activation, and it is facilitated through activation of JAKs; their findings indicated a role for TC-PTP in the negative regulation of cytokine signaling via its direct dephosphorylation of JAK1 and JAK3. JAK signaling is closely interconnected with STAT signaling. When cytokines or growth factors bind to their receptors, receptor-associated JAKs are activated and phosphorylate the receptors at specific residues. STATs are then recruited to bind to these sites in the active receptors and subsequently, JAKs phosphorylate STATs [37,38]. Ten Hoeve et al. were the first to identify STAT1 as a substrate of TC-PTP. They developed a PTPase assay through which they were able to observe STAT1 dephosphorylation and capture the PTP/STAT1 complex in HeLa cell nuclear extract. PTP was purified through chromatography and TC45 was identified by silver staining analysis [31]. Zu et al. further demonstrated that arginine methylation of STAT1 was required for TC-PTP dephosphorylation [39]. TC-PTP dephosphorylation of JAK1 and STAT1 also played a role in the negative regulation of INFγ signaling which is essential for the immune response [40,41]. Recent work by Manguso et al. utilizing the latest molecular biology technology, CRISPR-Cas9 genome editing, for loss-of-function screenings revealed deletion of *PTPN2* in tumors cells which were transplanted into mice enhanced sensitivity to immunotherapy due to the increase in STAT1 phosphorylation which resulted in increased INFγ signaling for the recruitment of T cells and antigen-presentation [42].

Within the STAT family of transcription factors STAT3 is the most well-known because it has been established as a major oncogenic protein that plays multifunctional roles in cell proliferation, autophagy, differentiation, and cell survival. It is mainly activated by the IL-6 family of cytokines, epidermal growth factor, and leptin [43–46]. Yamamoto et al. were the first to find that STAT3 is a substrate of TC-PTP. Multiple assays – luciferase reporter assay, co-immunoprecipitation assay with a substrate-trapping mutant, and GST-fusion protein pull-down assay – demonstrated TC45 directly bound to STAT3 to dephosphorylate it following cell stimulation with IL-6, and inactivation of STAT3 resulted in the inhibition of IL-6-mediated signaling which is an important mechanism in cellular processes such as the immune response [33]. On-going research continues to identify other potential substrates of TC-PTP including STAT6, vascular endothelial growth factor receptor, Met-receptor tyrosine kinase, Src tyrosine kinases, and caveolin-1 [47–53].

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TC-PTP-MEDIATED REGULATION OF CELLULAR FUNCTION IN CANCER CELLS

Many of the substrates negatively regulated by TC-PTP function in oncogenic mechanisms that promote cell growth and survival, like STAT3 signaling, or in mechanisms which lead to chemoresistance. For these reasons, there is evidence that TC-PTP can function as a tumor suppressor in different cancer types. For instance, focal deletion of *PTPN2* was detected in 6% of human T-cell acute lymphoblastic leukemias (T-ALL) and further functional analysis demonstrated TC-PTP reduces T cell proliferation through the down-regulation of JAK/STAT signaling [40,54]. Mutations in the JAK1 gene were shown to promote proliferation and survival of T-ALL cells. Findings revealed loss of *PTPN2* was concomitant with *JAK1* mutation in T-ALL, and the loss of TC-PTP caused lymphoid cells to be more susceptible to JAK1-mediated cellular transformation [41]. Similarly, Shields et al. reported a deficiency of TC-PTP in triple-negative primary breast cancer as well as a subset of breast cancer cell lines; loss of TC-PTP in the human breast cancer cell lines resulted in increased cell proliferation and anchorage-independent growth in vitro and in vivo xenograft model via reduced SFK (Src family protein tyrosine kinases) and STAT3 signaling [55]. Klingler-Hoffmann et al. found that TC-PTP could suppress the growth, proliferation, and tumorigenicity of glioblastoma in vitro and in vivo. TC45 dephosphorylated a truncated form of EGFR (ΔEGFR), which is a constitutively active form of EGFR that promotes glioblastoma growth. Dephosphorylation of ΔEGFR by TC45 resulted in inhibition of mitogen-activated protein kinase ERK2 but not PI3K signaling, suggesting that TC-PTP can suppress glioblastoma by negatively regulating ΔEGFR-mediated activation of ERK2 [56]. As previously mentioned, Wang et al. showed TC-PTP had tumor suppressive capabilities in colorectal cancer cells. GdX (X-linked gene in the *G6PD* cluster at Xq28) is a chaperon involved in protein processing in the ER. Their studies found that GdX was able to stabilize the steady-state association of phosphorylated STAT3 with TC45 to promote STAT3 dephosphorylation; consequently, deletion of *GdX* in mice significantly accelerated colitis-associated colorectal tumorigenesis which correlated with an increase in active STAT3 [57]. Recently, Grohmann et al. demonstrated that loss of TC-PTP in hepatocytes corresponded with increased STAT3 signaling, enhanced T cell recruitment, and development of hepatocellular carcinoma (HCC) in obese mice, and further studies showed deletion of TC-PTP in hepatocytes promoted HCC in mice exposed to HCC-inducing carcinogens, confirming TC-PTP can play a tumor suppressive role in HCC [58].

TC-PTP FUNCTION: LESSONS FROM MOUSE MODELS OF TC-PTP

Generation of TC-PTP-deficient mice showed that it has a critical role in hematopoiesis and immune function [59]. TC-PTP deletion in the germline produced progenies with Mendelian frequencies (1:2:1), indicating TC-PTP deficiency is not lethal in embryonic development. Newborn TC-PTP knockout homozygous (−/−) mice also did not demonstrate abnormalities in their physical appearance. However, by 2 weeks of age TC-PTP-deficient mice showed growth retardation and mortality by 3–5 weeks of age concomitant with runting, splenomegaly, and lymphadenopathy [59]. Further investigation revealed that the absence of TC-PTP in mice causes defects in the development of B cells and erythrocytes produced in

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bone marrow. TC-PTP deletion also impaired T cell function, without having an effect on T cell development, indicating a significant role for TC-PTP in both B and T cell functions [59]. Global deletion of TC-PTP in mice using Cre/LoxP recombination to delete both the *Ptpn2* gene and the neomycin resistance cassette further demonstrated the crucial role of TC-PTP in lymphocyte development [60]. In addition, generation of TC-PTP-deficient mice on two different backgrounds (BALB/c and C57BL/6) in this study showed that the effects of TC-PTP on morbidity, mortality, bone development, and the myeloid compartment were different between strains (Table 1).

Early lethality of TC-PTP knockout mice led to the development of targeted TC-PTP-deficient mouse models for cells or tissues such as T lymphocytes, neuron, pancreas, intestine and skin (Table 1). Specific deletion of TC-PTP in T cells resulted in the development of widespread inflammation and autoimmunity by reducing the threshold for T cell receptor-induced signaling in mice [51]. TC-PTP deficiency in neuronal cells of mice showed that loss of neuronal TC-PTP elevated leptin sensitivity and increased the resistance to high-fat-diet-induced weight gain, implying TC-PTP may play a role in obesity [61]. Pancreatic–specific TC-PTP deletion in mice demonstrated that TC-PTP could contribute to the progression of cerulean-induced acute pancreatitis by increasing the levels of inflammatory cytokines TNFα and IL-6 and NF-kB-mediated inflammation [62]. In regards to cancer, intestinal epithelial cell-specific deletion of TC-PTP led to an increase in colonic stem cell proliferation, resulting in elevated susceptibility to injuries, such as dextran sulphate sodium (DSS)-induced colitis, implying TC-PTP could serve as a tumor suppressor in colon cancer [63]. Global TC-PTP-deficient mice revealed that loss of TC-PTP in mammary fat pads resulted in a significant increase in both SFK and STAT3 signaling pathways, suggesting a tumor suppressive role for TC-PTP in breast cancer [55]. Collectively, the current research findings from in vivo studies have revealed that not only is TC-PTP a crucial modulator in immune functions, but it also may play an important role in the development of disease, including cancer. Although in vitro studies clearly have been useful in elucidating mechanisms through which TC-PTP mediates the suppression of cell proliferation and the promotion of apoptosis, more in vivo studies using tissue-specific TC-PTP mouse models are required to confirm and fully characterize the tumor suppressive function of TC-PTP in carcinogenesis.

ROLE OF TC-PTP IN ENVIRONMENTAL SKIN CARCINOGENESIS

The mouse model of multistage skin carcinogenesis is one well-defined experimental model for characterizing cellular, biochemical, and molecular mechanisms associated with different stages of epithelial carcinogenesis. Tumor development, which can be stimulated by either chemical exposure or UV irradiation, occurs via three distinct stages: initiation, promotion, and progression. During chemically-induced multistage skin carcinogenesis, tumor initiation is induced by a single topical dose of a genotoxic carcinogen, such as 7,12-dimethylbenz[a]anthracene (DMBA), which causes cellular transformation by generating a mutation in a critical gene, or genes, through the formation of specific carcinogen-DNA adducts. Transformed cells then undergo clonal expansion, increasing the probability of oncogenic genetic alteration in the expanded population, leading to the development of premalignant papillomas. Following tumor initiation, tumor promotion occurs by repeated

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treatment with a non-mutagenic tumor promoter, such as 12-*O*-tetradecanoylphorbol-13-acetate (TPA). TPA induces the expression of various genes encoding growth regulatory proteins, and it also activates many signaling proteins either via posttranslational modification or via direct stimulation of enzymatic activities, which results in enhanced epidermal cell proliferation and hyperplasia. During the tumor progression stage, the expanded population of transformed cells provides an advantageous selective pressure for the conversion of papillomas to malignant squamous cell carcinomas (SCCs), which occurs in a stochastic manner, independent of tumor promoter treatment [64,65]. During UV-induced multistage skin carcinogenesis, tumor development is similarly induced as described above, except UV radiation is used as both tumor initiator and promoter [66,67].

A variety of growth factor signaling pathways have been implicated in the development and progression of skin tumors. In particular, receptor tyrosine kinases (RTKs) such as the erbB family, insulin-like growth factor-1 receptor (IGF-1R), and c-met and their downstream signaling pathways (e.g. STAT3, PI3K/AKT/mTOR, and c-Src signaling) have been shown to be activated during skin carcinogenesis, which leads to increased epidermal proliferation and skin tumor formation [68]. Several studies have provided strong evidence that STAT3 especially is a critical oncogenic factor for skin tumor development induced by environmental carcinogens. It was revealed STAT3 is activated following treatment with tumor promoters including TPA in mouse epidermis, and it was constitutively activated in both papillomas and SCCs generated by DMBA/TPA, or two-stage, carcinogenesis regimen [69]. Studies utilizing keratinocyte-specific STAT3-deficient (*K5Cre.STAT3*$^{fl/fl}$) mice and transgenic mice expressing a constitutively active/dimerized form of STAT3 in keratinocytes (*K5.STAT3C*) demonstrated that STAT3 plays a critical role in epidermal cell survival and proliferation and in skin tumorigenesis [70,71]. STAT3-deficient mice were completely resistant to skin tumor development induced by two-stage carcinogenesis regimen [70]. STAT3-deficient mice were also resistant to UVB-induced skin carcinogenesis in that 95% of control wild-type mice developed tumors, whereas only 31% of STAT3-deficient mice developed tumors [72]. In contrast, *K5.STAT3C* mice were resistant to both two-stage and UVB-induced skin carcinogenesis as evidenced by a shortened latency of skin tumor development, demonstrating that activation of STAT3 enhanced skin cancer formation [71,72]. Generation of inducible STAT3-deficient mice further revealed that STAT3 was required for skin tumor development during both the initiation and promotion stages of skin carcinogenesis [73]. Additionally, targeted deletion of STAT3 in the bulge region of keratinocyte stem cells revealed that STAT3 was required for the survival of these cells during tumor initiation [74].

While the role of PTKs and their downstream signaling pathways in skin carcinogenesis has been widely studied, the potential role(s) of PTPs remain to be determined. Initial research revealed that the expression level of PTPs remained unchanged in the epidermis, even though PTP expression was induced during keratinocyte proliferation and maturation [75]. Biochemical studies demonstrated that reactive oxygen species (such as H_2O_2) produced by UV irradiation or chemical treatment resulted in the inactivation of PTPs via oxidation of the cysteine residue within the conserved active-site of the PTP catalytic domain [76–78]. Additional work confirmed that acute UV irradiation could induce inactivation of PTPs, such as receptor-type PTP kappa, in keratinocytes [79,80]. These findings suggested that

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PTPs might not play a significant, unique function in the cell response to skin cancer inducers given that they are inactivated. However, we have contributed a great deal of work demonstrating that TC-PTP is activated by UV radiation and chemical toxicants and consequently, its plays an important tumor suppressive role during skin carcinogenesis. First, our studies showed UVB irradiation triggered PTP to inactivate STAT3 in skin [81]. Further analysis revealed TC-PTP, SHP1, and SHP2, are three PTPs that cooperated to dephosphorylate STAT3 in response to UVB radiation [82]. Knockdown of PTP expression with siRNA demonstrated that loss of TC-PTP had a more significant effect on expression levels of active STAT3 in keratinocytes compared to loss of either SHP1 or SHP2 in the absence or presence of UVB irradiation, and this result corresponded with a significantly increased cell proliferation. These findings identified TC-PTP as the primary PTP involved in the regulation of STAT3 signaling during the keratinocyte response to UVB exposure [83].

Similar to UVB irradiation, we found TPA treatment elicited PTP-mediated STAT3 dephosphorylation in keratinocytes in a dose-dependent manner, whereas TC-PTP knockdown reversed this effect. Therefore, we hypothesized that TC-PTP-mediated STAT3 dephosphorylation might be a critical step in a general protective mechanism in skin that is triggered by environmental assault from agents such as UV radiation or chemical toxicant. Interestingly, we also found that TC-PTP activation could continue to occur upon each exposure to TPA treatment. We demonstrated expression levels of active STAT3 gradually recovered 8 hours after a single treatment of TPA; however, re-treatment of cells with TPA for 3 hours decreased phosphorylated STAT3 levels again. This effect was not observed in TC-PTP knockdown keratinocytes, indicating TC-PTP was a major modulator in the regulation of STAT3 signaling, especially in response to chemical exposure, such as TPA [84].

To further characterize the role of TC-PTP in our hypothesized skin protective mechanism, we utilized an epidermal specific TC-PTP-deficient (*K14Cre.Ptpn2*$^{fl/fl}$) mouse model generated using the Cre-LoxP system. Morphological differences in the epidermis were not observed between wild-type and TC-PTP-deficient mice. However, we found DMBA-induced epidermal apoptosis was significantly reduced in TC-PTP-deficient mice compared to wild-type mice. In addition, TPA-induced keratinocyte proliferation and epidermal hyperplasia were significantly increased in TC-PTP-deficient mice compared to control mice. These results corresponded with significantly increased expression levels of active STAT3 and AKT as demonstrated by western blot analysis. Inhibition of STAT3 or AKT before DMBA or TPA treatment increased sensitivity to DMBA-induced apoptosis and reduced TPA-induced cell proliferation in TC-PTP-deficient keratinocytes in comparison to control. Our findings implied that TC-PTP promotes apoptosis to eliminate DMBA or TPA damaged keratinocytes via the negative regulation of STAT3 and AKT signaling (Figure 1) and thereby, may function as a tumor suppressor by preventing the accumulation of deleterious mutations during tumor initiation and promotion. Consistent with these results, TC-PTP-deficient mice presented significantly increased numbers of tumors and a shortened latency of tumorigenesis during two-stage skin carcinogenesis [84].

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Furthermore, we found TC-PTP-deficient mice exhibited significantly increased epidermal thickness and hyperplasia following UVB irradiation in comparison to control mice (unpublished), implying that TC-PTP may play a tumor suppressive role in UVB-induced skin carcinogenesis. We revealed TC-PTP deficiency in mouse epidermis significantly reduced UVB-induced apoptosis which corresponded with increased fetal liver kinase-1 (Flk-1, also known as vascular endothelial growth factor receptor 2 (VEGFR2))/JNK signaling. Flk-1 contains seven potential tyrosine phosphorylation sites, and we found the level of phosphorylated Flk-1 at tyrosine residue 1173 (Y1173, Y1175 in human) was significantly increased in TC-PTP-deficient keratinocytes after UVB exposure, corresponding with increased resistance to UVB-induced apoptosis compared to control cells. Use of a TC-PTP substrate-trapping mutant TC-PTP-D182A confirmed that TC-PTP dephosphorylated Flk-1 by direct interaction. Loss of TC-PTP not only resulted in the activation of Flk-1, but it also resulted in a significantly increased level of JNK phosphorylation. Treatment with either Flk-1 or JNK inhibitor reversed the effect of TC-PTP deficiency, illustrating that TC-PTP could facilitate UVB-induced apoptosis by negatively regulating Flk-1/JNK-dependent cell survival signaling [53] (Figure 1). Collectively, these results indicated that TC-PTP plays a critical role in skin carcinogenesis induced by environmental factors.

CONCLUSIONS

PTPs have been implicated in carcinogenesis as either tumor suppressors or tumor promoters. Studies have shown that TC-PTP appears to have a tumor suppressive function in several types of cancers including leukemia, breast cancer, and colon cancer mainly through its negative regulation of STAT3 oncogenic signaling. Recent studies using an epidermal-specific TC-PTP-deficient mouse model in multistage skin carcinogenesis bioassays have provided strong evidence that TC-PTP can contribute to the suppression of skin tumor development by downregulating two oncogenic signaling pathways, STAT3 and AKT signaling, during tumor initiation and promotion stages. TC-PTP may also contribute to the suppression of UVB-induced skin cancer development by promoting apoptosis and suppressing cell proliferation via UVB-mediated nuclear translocation of TC-PTP, which results in the dephosphorylation of STAT3 in the keratinocyte nucleus, and via negative regulation of Flk-1/JNK signaling in the cytoplasm of keratinocytes. It is possible that TC-PTP also can contribute to suppressing tumor progression by dephosphorylating other unknown substrate target(s). These findings characterizing the tumor suppressive function of TC-PTP during skin carcinogenesis suggest that induction of TC-PTP activity and/or stimulation of its activators may be a novel therapeutic strategy for the prevention of SCC and potentially other epithelial cancers. As previously mentioned, Manguso et al. revealed deletion of *PTPN2* in melanoma and colon carcinoma cells enhanced sensitivity to immunotherapy, indicating that in this case, overexpression of TC-PTP would be detrimental to cancer treatment. Therefore, more research is needed to fully elucidate at what stage of tumorigenesis TC-PTP may be targeted for either activation or inhibition and/or which strategy would be the most clinically effective based on cancer type.

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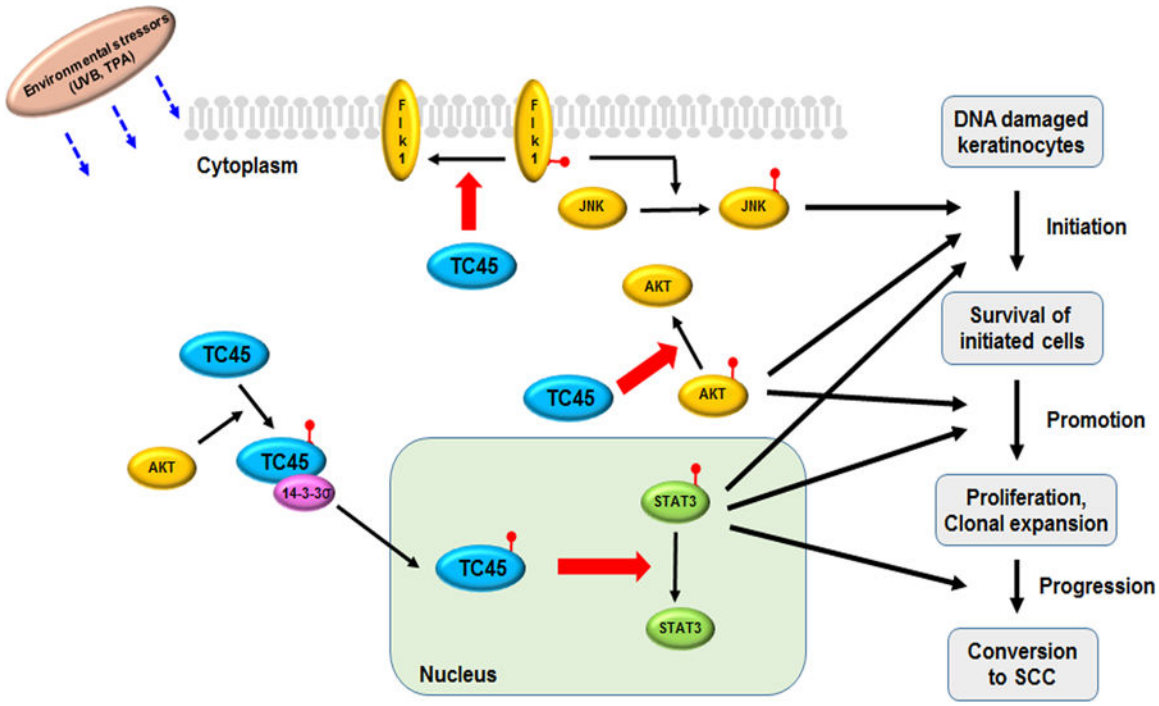

Figure 1. The mechanisms of TC-PTP-mediated regulation of epidermal cell survival and proliferations against environmental stressors.

In response to environmental stressors, such as UVB irradiation or TPA treatment, TC45, one isoform of TC-PTP, promotes apoptosis and inhibits keratinocyte proliferation by negatively regulating STAT3 and AKT signaling pathways. UVB- or TPA-induced nuclear translocation of TC45 by the AKT/14–3-3σ axis contributes to the enhanced STAT3 dephosphorylation. TC45 also contributes to increased epidermal apoptosis following UVB exposure by the dephosphorylation of Flk-1 and subsequent downregulation of JNK signaling. Collectively, TC-PTP can attenuate skin tumor development induced by environmental stressors as part of an initial protective mechanism.

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Table 1.

TC-PTP Knockout mouse models

Tissue/Cell	Phenotype	Reference
Whole tissue	Early lethality, splenomegaly, lymphadenopathy Impaired T and B cell functions	[59]
Whole tissue	Early lethality, defects on lymphocyte development Impaired myeloid and bone development (strain dependent)	[60]
T cell	Development of widespread inflammation and autoimmunity	[51]
Neuron	Elevated leptin sensitivity Resistant to high-fat-diet-induced weight gain	[61]
Pancreas	Reduction in cerulean-induced pancreatitis	[62]
Intestinal epithelium	Increase in colonic stem cell proliferation Elevated susceptibility in DSS-induced colitis	[63]
Epidermis	Enhanced skin tumor formation in two-stage carcinogenesis	[84]