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Review

Protein Tyrosine Phosphatases as Potential Regulators of STAT3 Signaling

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Abstract: The signal transducer and activator of transcription 3 (STAT3) protein is a major transcription factor involved in many cellular processes, such as cell growth and proliferation, differentiation, migration, and cell death or cell apoptosis. It is activated in response to a variety of extracellular stimuli including cytokines and growth factors. The aberrant activation of STAT3 contributes to several human diseases, particularly cancer. Consequently, STAT3-mediated signaling continues to be extensively studied in order to identify potential targets for the development of new and more effective clinical therapeutics. STAT3 activation can be regulated, either positively or negatively, by different posttranslational mechanisms including serine or tyrosine phosphorylation/dephosphorylation, acetylation, or demethylation. One of the major mechanisms that negatively regulates STAT3 activation is dephosphorylation of the tyrosine residue essential for its activation by protein tyrosine phosphatases (PTPs). There are seven PTPs that have been shown to dephosphorylate STAT3 and, thereby, regulate STAT3 signaling: PTP receptor-type D (PTPRD), PTP receptor-type T (PTPRT), PTP receptor-type K (PTPRK), Src homology region 2 (SH-2) domain-containing phosphatase 1(SHP1), SH-2 domain-containing phosphatase 2 (SHP2), MEG2/PTP non-receptor type 9 (PTPN9), and T-cell PTP (TC-PTP)/PTP non-receptor type 2 (PTPN2). These regulators have great potential as targets for the development of more effective therapies against human disease, including cancer.

Keywords: STAT3; PTPRT; PTPRD; SHP1; SHP2; TC-PTP

1. Introduction

The signal transducer and activator of transcription (STAT) protein family includes intracellular latent transcription factors that facilitate the cellular signaling initiated by stimuli from growth factors and cytokines that is required for multiple key cellular processes. Currently, there are seven known members of the STAT family in humans: STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, and STAT6. Signal transducer and activator of transcription 3 (STAT3, encoded by the *STAT3* gene) is the most

prominent of all the STATs, because it has been established as a major oncogenic protein. In a majority of cancers, it is constitutively activated at tyrosine 705 (Y705), which disrupts mechanisms involved in cell proliferation, autophagy, differentiation, and/or cell survival, depending on the cell type [1–3].

All the STATs are composed of six conserved domains: an N-terminal domain, a coiled-coil domain, a DNA-binding domain, a linker domain, a Src homology region 2 (SH-2) domain, and a C-terminal transactivation domain. Alternative splicing produces two active isoforms of STAT3: the full-length form, referred to as STAT3α, and a truncated form named STAT3β, which lacks approximately 55 bases pairs within the C-terminal domain (Figure 1) [4,5]. STATs are activated by phosphorylation at a tyrosine residue (Y) and at a serine residue (S) within the transactivation domain. Once activated, a STAT makes a reversible binding with specific tyrosine residues on active cytokine or growth factor receptors through its SH-2 domain, which permits the Janus-activated kinases (JAKs) to facilitate tyrosine phosphorylation of the STAT. Phosphorylation triggers STAT dimerization by reciprocal phosphotyrosine–SH-2 interactions to form stable "parallel" dimers. The active STAT dimers can then be translocated into the nucleus where they bind to DNA elements within target genes to regulate transcriptional expression. All the STATs, except for STAT2, recognize consensus palindromic sequences (TTCN$_x$GAA, where x = 2–6 nucleotides), known as γ interferon activation sites (GAS), within the gene promoter, and these sites determine the specificity of the STAT that binds to the promoter; for example, if the GAS has an x of N equal to 4, then STAT3 can bind more efficiently [3,6–9].

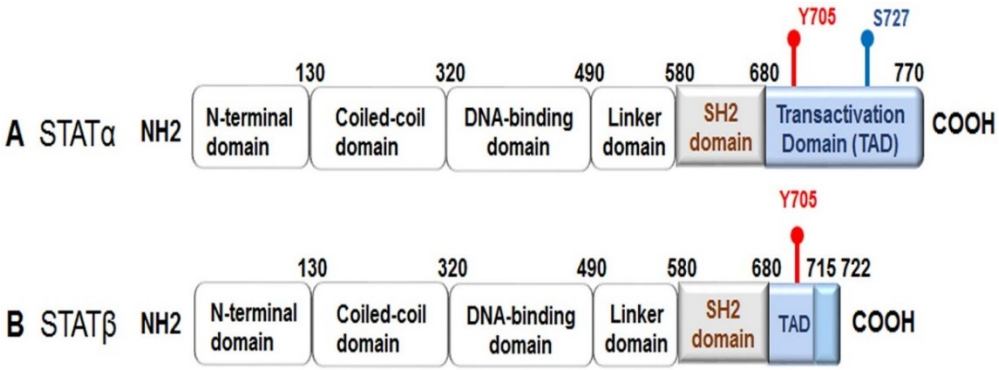

Figure 1. Schematic of the full-length signal transducer and activator of transcription 3 (STAT3) protein structure. STAT3 is comprised of six conserved domains: an N-terminal domain, a coiled-coil domain, a DNA-binding domain, a linker domain, a Src homology region 2 (SH-2) domain, and a C-terminal transactivation domain. The transactivation domain contains two phosphorylation (P) sites: a tyrosine residue (Y) at 705, which is required for STAT3 activation, and a serine residue (S) at 727. Once STAT3 is activated, the P(Y)–SH-2 domains interact to form a STAT3 dimer. (**A**) STAT3α, the full-length form of STAT3; (**B**) STAT3β is a C-terminal truncated form of STAT3 generated by an alternative splicing. STAT3β does not contain a serine phosphorylation site at 727.

As previously mentioned, STAT3 is activated following phosphorylation at Y705 (Figure 1). STAT3 activation also can occur via phosphorylation of S727 by mitogen-activated protein kinases (MAPKs) or c-Src non-receptor tyrosine kinase [10,11]. Serine phosphorylation of STAT3 promotes transactivation [5,12,13]. Furthermore, it has been demonstrated that phosphorylated STAT3 (S727) can be transported into the mitochondria instead of the nucleus, where it contributes to cellular homeostasis by modulating the optimal function of the electron transport chain [14–17]. Interestingly, STAT3β lacks S727, and due to this truncation, it has been regarded as a dominant negative form; however, evidence from functional in vivo studies has revealed that STAT3β can not only activate STAT3 target genes, but it also plays a role in inflammation [5].

The rate and duration of phosphotyrosine-based signaling, such as the JAK-mediated activation of STAT3, is maintained by the activities of protein tyrosine phosphatases (PTPs). PTPs are a large and diverse family of enzymes, which catalyze the removal of the phosphate group from the tyrosine residue of phosphorylated proteins [18–21]. Despite the importance of PTPs in the regulation of

STAT signaling, particularly in the development of a variety of human diseases, such as cancer, the relationship between PTPs and STATs has still not been completely characterized. Here, we will review the PTPs that have been implicated in the inactivation of STAT3, with an emphasis on PTP regulation of STAT3 signaling in cancer.

2. Protein Tyrosine Phosphatase Receptor-Type D

PTP receptor-type D or PTPRD (PTPδ) is a member of the highly conserved family of receptor PTPs that is encoded by the *PTPRD* gene. It is classified as a member of the LAR subfamily of transmembrane PTPs, which includes LAR and PTPσ (PTPRS) [22,23]. PTPRD is a transmembrane protein composed of an extracellular region, which possesses three Ig-like and eight fibronectin-type III-like domains, a single transmembrane region, and two tandem intracytoplasmic catalytic domains, referred to as D1 and D2. The extracellular region is similar in structure to cell adhesion molecules, implying that PTPRD, and other receptor-type PTPs like it, have similar ligands and functions [23,24]. In fact, PTPRD is known to be a ligand for cell adhesion and neurite outgrowth, and different truncated isoforms can be produced through alternative splicing, depending on the requirements of the different tissue and developmental stages [25]. PTPRD is expressed in astrocytes and tissue, such as brain, colon, and breast tissues [26].

Receptor-type PTPs have been shown to be inactivated in a number of human cancers, implying that these PTPs have tumor suppressive capabilities. The *PTPRD* gene, specifically, is frequently inactivated by genetic (deletion, mutation, copy number loss) or epigenetic (hypermethylation) mechanisms in cancers, such as glioblastoma multiforme (GBM), colon cancer, breast cancer, neuroblastoma, lung cancer, and squamous cell carcinoma (SCC) [24,26–32]. These findings indicate that PTPRD is a major tumor suppressor, and in fact, functional studies have revealed that PTPRD-deficiency enhanced the tumor-forming capability of immortalized human astrocytes in mouse xenograft models [26]. Another study showed that homozygous or heterozygous deletion of *Ptprd* in the absence of *Cdkn2a*, a gene that encodes the tumor suppressors $p16^{Ink4}$ and $p14/p19^{Arf}$, resulted in increased tumorigenesis in comparison to mice with *Cdkn2a* deletion alone, and *Ptprd*-deficiency may influence which types of tumors form [30]. PTPRD cooperates with CD44 and β-catenin/TCF signaling to regulate cell migration and progression in colon cancer [24]. CD44 is a major cell-surface glycoprotein, critical to cancer invasion and metastasis, which can function as a marker for cancer stem cells, cells that can give rise to the many cell types that form tumors. Additionally, it has been shown that the exogenous expression of PTPRD in PTPRD-deficient primary melanoma cells significantly decreased cell growth and cell viability, and it yielded an increase in apoptosis in a time-dependent manner; however, the expression of PTPRD containing cancer-specific mutations reversed this effect [29].

PTPRD is capable of directly interacting with PTPRS [22], the cytoskeletal remodeling proteins liprin-α-1 and MIM (Missing in Metastasis) [23,24], and STAT3 [26,30,33], which suggests that PTPRD may play a functional role in cancer cell survival, adhesion, and/or migration through the signaling mechanisms mediated by these substrates. Veeriah et al. demonstrated that PTPRD acts as a tumor suppressor through its ability to negatively regulate STAT3-mediated signaling [26]. The exogenous expression of PTPRD in human GBM and other cancer cell lines inhibited cell growth, which coincided with a substantial decrease in the expression levels of phosphorylated STAT3 (Y705) and, consequently, one of its downstream targets, suppressor of cytokine signaling 3 (SOCS3) [26]. However, the expression of PTPRD containing cancer-specific mutations reversed the inhibitory effect on cell growth and STAT3 phosphorylation. Immunoprecipitation assays confirmed that PTPRD directly interacts with STAT3 [26]. Heterologous loss of *Ptprd* or *PTPRD* is sufficient to see a significant increase in STAT3 phosphorylation and an upregulation of STAT3 target genes within GBM tumors [30]. Loss-of-function mutations in *PTPRD* contribute to enhanced cell growth and increased levels of phosphorylated STAT3 (Y705) in head and neck SCC cells [31]. Interestingly, head and neck SCC cells containing a *PTPRD*

mutation were more susceptible to a STAT3 inhibitor, suggesting that use of this type of anti-cancer drug could be utilized for more successful treatments of head and neck SCC patients [31].

3. Protein Tyrosine Phosphatase Receptor-Type T

PTP receptor-type T (PTPRT), alternatively known as PTPρ, is another receptor PTP that belongs to the type IIB receptor-type (R2A) PTP subfamily, which also includes PTPRK (PTPκ), PTPRM (PTPμ), and PTPRU (otherwise known as PCP-2). It is composed of an extracellular domain containing a MAM (meprin/A5/PTPμ) domain and an Ig domain and four fibronectin-type III repeats, a transmembrane domain, a juxtamembrane region, and two phosphatase domains, referred to as D1 and D2. Primarily, D1 is responsible for the catalytic activity of PTPRT, whereas D2 is more important for regulation [34]. PTPRT is largely expressed in the brain and spinal cord. It plays a role in cell adhesion through its extracellular domain [35–37], and it serves an important function in neurological development. For instance, PTPRT has been shown to directly dephosphorylate E-cadherin at intercellular adheren junctions to regulate hemophilic cell–cell adhesion in the central nervous system [38]. Also, it stimulates synapse formation through its interaction with neuroligin and neurexin, proteins that connect and maintain the synapse between neurons [39].

Like PTPRD, PTPRT is inactivated by mutation in many cancers, including lung cancer, gastric cancer, and head and neck SCC, and it is most frequently mutated in colorectal cancer (CRC) [40–43]. Mutations in *PTPRT* consist of nonsense, insertion, and deletion mutations, with the majority being missense mutations. Missense mutations in the catalytic domain have been implicated in reducing its phosphatase activity, and mutations in the extracellular domain impair its function in cell adhesion [35,42,44]. PTPRT can function as a tumor suppressor through its interaction with its substrates, paxillin and STAT3 [40,41]. The knockout of PTPRT has resulted in increased colon tumor formation in a mouse model, which correlates with increased paxillin phosphorylation [44]. The activation of paxillin triggers the activation of AKT (protein kinase B), a major kinase involved in oncogenic signaling. Zhang et al. [41] demonstrated that PTPRT negatively regulates STAT3-mediated signaling by directly dephosphorylating STAT3 at Y705, which prohibits STAT3 nuclear translocation, resulting in a variety of effects depending on the cancer type. Whole exome sequencing and reverse-phase protein array analysis showed that *PTPRT* mutations are associated with increased STAT3 activation in head and neck SCC, leading to increased cell survival and, therefore, may serve as a biomarker to predict the efficacy of STAT3 inhibitors as a chemotherapeutic [43]. Many human cancers show aberrant hypermethylation of the *PTPRT* promoter, which results in the decreased expression of *PTPRT* mRNA [45]. Peyser et al. [45] showed that this decrease correlated with an increase in phosphorylated STAT3 in head and neck SCC and sensitivity to STAT3 inhibition. These findings suggest that *PTPRT* hypermethylation could also function as a biomarker for the efficacy of STAT3 inhibitors against cancer. Furthermore, it has been shown that post-translational modification of PTPRT by glycosylation reduces its activity by causing it to dimerize, which has been shown to result in enhanced cancer cell migration via the activation of STAT3-mediated signaling [46].

4. Protein Tyrosine Phosphatase Receptor-Type K

As previously mentioned, PTPRK (encoded by *PTPRK*) is a R2A subfamily member with PTPRT, and it functions in homophilic binding via its extracellular domain [47]. PTPRK is expressed in the cytoplasm of different tissues and cell types, including the central nervous system and human keratinocytes [48]. It has been shown to mediate neurite outgrowth via a Grb2/MEK1-dependent signaling pathway and T-cell development [49,50]. In keratinocytes, transforming growth factor β1 (TGF-β1) inhibits cell proliferation and triggers cell migration through the upregulation of PTPRK [48]. Additionally, PTPRK was found to co-localize with β-catenin at adherens junctions, suggesting that PTPRK plays a role in cell contact and adhesion, such as PTPRD and PTPRT [51,52]. Indeed, further studies have demonstrated, for example, that PTPRK negatively regulated adhesion and invasion in breast cancer cells [53]. The expression of *PTPRK* mRNA transcript was reduced in the primary

tumors harvested from breast cancer patients with metastatic tumors or who had succumbed to the disease. Furthermore, patients who expressed higher levels of *PTPRK* survived longer than patients with low levels. In vitro studies confirmed that the knockdown of PTPRK increased cell proliferation, adhesion, and invasion, suggesting it functions as a tumor suppressor in breast cancer [53]. PTPRK has also been shown to act as a tumor suppressor in central nervous system lymphomas, CRC, and prostate cancer [54–56]. The use of mapping arrays revealed that genetic alterations (gene deletion and missense mutations) of *PTPRK* could be found in glioma biopsies, and they disrupt PTPRK activity and post-translational regulation [57].

Some major substrates of PTPRK that have been identified are epidermal growth factor receptor (EGFR) and STAT3. PTPRK can directly dephosphorylate EGFR during both basal- and ligand-stimulated EGFR phosphorylation, and it can contribute to tumor suppression through its negative regulation of EGFR signaling [58–60]. Chen et al. were the first to demonstrate that PTPRK directly interacts with and dephosphorylates active STAT3 at Y705 [61]. Their studies revealed that the expression of PTPRK was decreased in nasal-type natural killer T-cell lymphoma (NKTCL) human cell lines and primary tumors, and this decrease was inversely correlated with phosphorylated STAT3 (Y705) expression; the knockdown of PTPRK further decreased the expression levels of phosphorylated STAT3, whereas the overexpression of PTPRK reversed this effect, which resulted in increased NKTCL cell growth and invasion [61]. Additionally, Chen et al. [61] found that decreased PTPRK expression was a result of decreased PTPRK mRNA levels due to monoallelic deletion and promoter hypermethylation, and these genetic alterations were associated with a poor prognosis for NKTCL patients undergoing standard treatment.

5. Src Homology Region 2 Domain-Containing Phosphatase 1

Src homology region 2 (SH-2) domain-containing phosphatase 1, or SHP1, is a non-receptor PTP encoded by *PTPN6*. SHP1 is a member of a subfamily of non-transmembrane PTPs that are composed of two tandem N-terminal Src homolog domains (N-SH2 and D-SH2), a classic catalytic PTP domain, and a C-terminal tail containing two sites for tyrosine phosphorylation and a nuclear localization signal [62–64]. There are two forms of SHP1, which differ by their N-terminal amino acid sequences: form I contains MLSRG, and form II contains MVR. The expression of these isoforms are regulated by either promoter 1, which is found in nonhematopoietic-derived cells, or promoter 2, which is exclusively active in hematopoietic-derived cells [65]. SHP1 is most abundantly expressed in the nucleus of epithelial cells and the cytoplasm of hematopoietic cells, although stimulation by cytokines can induce nuclear translocation of SHP1 in hemopoietic cells [63]. The binding of SHP1 at its N-terminal SH-2 domain to a specific motif—the immune-receptor tyrosine-based inhibitory motif (IVLxYxxIVL)—in receptors, scaffold adapters, or immune inhibitory receptors causes a conformational change that actives SHP1 by exposing its active site to its substrates [63,66]. The modification of the C-terminal tail by truncation, phospholipid binding, or tyrosine phosphorylation has been implicated in the regulation of SHP1 phosphatase activity, and moreover, it was shown that Src kinase is one kinase that phosphorylates SHP1 in order to allow SHP1 to more readily dephosphorylate Src-activated substrates [67]. SHP1 is a major negative regulator of cytokine-mediated signaling pathways, such as inflammatory protein interleukin (IL)-3 receptor signaling and epidermal growth factor (EGF) signaling, in lymphocytes, which facilitate lymphocyte activation for cell proliferation and differentiation [66,68]. On the other hand, SHP1 has been implicated in the positive regulation of glia cell differentiation and Ras-dependent MAPK activation [67].

The downregulation or loss of SHP1 protein expression is a characteristic of human lymphoma and leukemia, and in fact, methylation of the *PTPN6* promoter, resulting in suppressed SHP1 expression, was found in anaplastic large cell lymphoma (ALCL), multiple myeloma, T-cell lymphoma, and B-cell lymphoma [68–74]. STAT3 and DNA methyltransferase 1 appear to function cooperatively to promote this epigenetic silencing in T-cell lymphoma [74]. Additionally, a recent study identified loss-of-function point mutations within *PTPN6* in diffuse large B-cell lymphoma [75]. Altered SHP1

expression has also been noted in breast, ovarian, prostate, and pancreatic cancers [65]. The tumor suppressive capability of SHP1 occurs through its regulation of JAK and STAT. For example, Han et al. [68] demonstrated that overexpression of SHP1 in ALK+ ALCL cells—a distinct type of non-Hodgkin lymphoma—which are deficient in SHP1, reversed JAK3 and STAT3 activation, which corresponded with a decrease in STAT3 targets. It was also shown that SHP1 downregulates JAK3 via increased proteasome degradation [68]. Research into the chemotherapeutic properties of various compounds have revealed the importance of SHP1 regulation of JAK/STAT signaling in the efficacy of these compounds. Guggulsterone (GS), a phytosteroid extracted from the guggul plant, can induce apoptosis and suppress the proliferation of multiple cancer types, such as leukemia, head and neck SCC, and melanoma. Ahn et al. demonstrated that GS induces SHP1 expression, which resulted in the inhibition of JAK2 activation and markedly decreased STAT3 phosphorylation [76]. Dovitinib, a multi-targeted receptor kinase inhibitor, was shown to directly and effectively induce SHP1 activity, leading to decreased STAT3 phosphorylation, the inhibition of hepatocellular carcinoma (HCC) growth, and an increase in apoptosis [77]. These findings further implied that the use of dovitinib in combination with the current clinical drug, sorafenib, could help overcome chemoresistance in HCC. However, a recent study was able to generate sorafenib derivatives that more effectively activate SHP1 activity and, thereby, inhibit STAT3 activation and suppress cancer cell growth to combat tumorigenesis and chemoresistance [78]. Plumbagin, a vitamin K3 analogue derived from a medicinal plant, induces the expression of SHP1 in human multiple myeloma cells, which resulted in the inhibition of STAT3 phosphorylation via the inactivation of c-Src, JAK1, and JAK2 [79]. In epidermal keratinocytes, SHP1 is initially activated in response to ultraviolet B (UVB) exposure and contributes to reduced STAT3 phosphorylation in cooperation with other PTPs, Src homology region 2 domain-containing phosphatase-2 (SHP2) and T-cell PTP (TC-PTP), implying that SHP1 is involved in an initial protective mechanism against UVB-induced skin cancer formation [80].

It is important to note that the modulation of SHP1 expression can play a role in noncancerous disease as well. Ruchusatsawat et al. [81] revealed that the *PTPN6* promoter 2 is methylated in normal epithelial cells and tissues to repress SHP1 expression; however, a significant increase in demethylation was observed in psoriatic skin lesions, resulting in the expression of SHP1 isoform II. Psoriasis is a T-cell mediated disease that involves the dysregulation of MAPK and JAK/STAT signaling [81]. Another study has shown that SHP1 deficiency in mice resulted in inflammatory skin disease due to abnormal toll-like receptor (TLR) activation leading to increased IL-1β production in neutrophils [82].

Along with STAT3, SHP1 has been reported to regulate STAT5 and STAT6. STAT5 plays a role in many hematopoietic malignancies. For example, SHP1 mRNA and protein levels were found to be significantly reduced in patients with chronic myelogenous leukemia as a result of hypermethylation of the *PTPN6* promoter, and an in vitro study revealed that the overexpression of SHP1 negatively regulated several signaling pathways, including JAK2/STAT5 signaling [83]. Another recent study showed that phospholipase C β3 (PLC-β3) recruits SHP1 and STAT5 to its C-terminal domain to facilitate the dephosphorylation of STAT5, which inhibits cell proliferation, survival, and differentiation, leading to the suppression of myeloproliferative disease, lymphoma, and other tumors in PLC-β3 knockout mice [84]. Interestingly, PLC-β3 knockout mice can spontaneously develop atopic dermatitis-like skin lesions and severe allergen-induced dermatitis, and these symptoms required the presence of mast cells [85]. These mast cells were sensitive to IL-3 stimulation due to the increased STAT5 activation, which could be reversed by SHP1. STAT6 is involved in IL-4-mediated cellular processes, and SHP1 has been shown to regulate IL-4 induction of STAT6 activation, which may contribute to T-cell homeostasis [86–88].

6. Src Homology Region 2 Domain-Containing Phosphatase-2

SHP2 is a ubiquitously expressed, cytosolic non-receptor PTP, encoded by *PTPN11*. It has an identical structure to SHP1 except that its C-terminal tail contains proline-rich domains instead of a nuclear localization sequence (NLS). So, as with SHP1, it is auto-inhibited by the N-terminal SH-2

domains [63]. SHP2 functions as a major regulator of the cell signaling required for cell growth, transformation, differentiation, spreading, migration, and cytoskeleton organization [89–91]. It enhances signal transduction through its interactions with different growth factors, scaffolding adaptors, cytokines, and extracellular matrix receptors that possess a SH-2 domain [89,91]. In particular, SHP2 is required for the activation of the Ras GTPase/extracellular signal-regulated kinase (ERK) signaling cascade [90–92]. The exact mechanism of activation remains unclear; however, it is known that ERK activation results in the inactivation of the pro-apoptotic proteins Bim (Bcl-2-like protein 11) and BAD (Bcl-2-associated death promoter), members of the Bcl-2 family of proteins. It also has been implicated in the regulation of the Phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K)/AKT pathway, which results in the promotion of cell survival through the suppression of caspase 3-mediated apoptosis [93].

Germline gain-of-function mutations of *PTPN11* cause ~50% of the cases of the genetic disease Noonan Syndrome, a disorder that causes abnormal development in different parts of the body and is associated with the increased risk of malignancy and leukemia [90–92,94]. The rare genetic disease LEOPARD syndrome, a variant of Noonan Syndrome, given the similarities in characteristic symptoms, is also caused by germline mutations in *PTPN11*; however, these missense mutations inactivate SHP2 [94]. SHP2 has been established as a major oncogenic protein, and in fact, *PTPN11* was the first proto-oncogene identified to encode a tyrosine phosphatase [95]. PTPN11 mutations have been identified in lung, breast, and colon cancer, leukemia, neuroblastoma, and melanoma. The dysregulation of SHP2 in cancer cells has been implicated to play a role in tumor invasion and metastasis, apoptosis, cell proliferation, DNA damage repair, and chemoresistance [90,92,96].

Given that SHP2 is primarily known to promote cancer, it seems counter-intuitive that it would function to dephosphorylate STAT3; however, some studies have revealed that SHP2 shows some tumor suppressive capabilities through its inactivation of STAT3. Bard-Chapeau et al. [97] demonstrated that the knockout of SHP2 in hepatocytes of mice caused liver inflammation and necrosis, leading to nodular regenerative hyperplasia. SHP2-deficient mice also presented an increase in spontaneous hepatocellular adenomas and chemically-induced HCCs as a result of an increase in STAT3-mediated inflammatory signaling. In agreement with these findings, SHP2 is downregulated in a small population of human HCCs [97]. Another study showed that SHP2 expression is also repressed in human esophageal squamous cell cancer (ESCC), and SHP2 knockdown results in increased ESCC cell proliferation in vitro and in vivo, which corresponded with a significant increase in phosphorylated STAT3 [98]. Moreover, Huang et al. [99] demonstrated that SHP2 inhibition of colorectal cancer cell proliferation and migration corresponded with the negative regulation of STAT3 by SHP2; more importantly, low expression levels of SHP2 and high expression levels of phosphorylated STAT3 were associated with poor patient prognosis and vice versa. As mentioned above, SHP2 has been shown to cooperate with SHP1 and TC-PTP to dephosphorylate STAT3 in response to UV irradiation as part of an initial protective response against skin carcinogenesis [80]. Additionally, in melanoma cells, the loss of glucose-phosphate dehydrogenase, a key metabolic enzyme that is highly expressed in different cancers, and NADPH oxidase 4 inhibit cell proliferation via the suppression of SHP2 and Src, which regulate STAT3 activation and DNA binding activity, respectively [100].

SHP2 has also been implicated in the regulation of STAT1 and STAT5. STAT1 mediates various biological functions in normal cells, such as cell death, cell growth inhibition, immune system stimulation, and cell differentiation regulation [101]. The knockout of SHP2 in mouse fibroblast cells resulted in enhanced and prolonged STAT1 phosphorylation at both Y701 and S727, induced by interferon (IFN) γ, and an immunoprecipitation assay confirmed that SHP2 interacts directly with STAT1 to negatively regulate it [102]. Interestingly, STAT1 is primarily considered to be a tumor suppressor. Consistent with this hypothesis, Liu et al. found that SHP2 expression is high in human prostate cancer cell lines, which coincided with low STAT1 phosphorylation and decreased T-cell activation [103]. Additionally, SHP2 expression is upregulated in human head and neck cancer tissue, and an in vitro study showed that the loss of SHP2 promoted STAT1 activation, which reduced human leukocyte antigen class I levels, leading to secretion of inflammatory, T-cell-attracting chemokines [104].

With regards to STAT5, Chen et al. demonstrated that SHP2—and not SHP1—directly accelerates the dephosphorylation of STAT5a [105]. It was also demonstrated that a SHP2 deficiency in human $CD34^+$ hematopoietic progenitor cells significantly inhibited growth factor-mediated cell survival, proliferation, and differentiation via the downregulation of ERK1/2, AKT, and JAK/STAT5 signaling [83].

7. MEG2/Protein Tyrosine Phosphatase Non-Receptor Type 9

PTP non-receptor type 9, otherwise known as PTP-MEG2 or simply, MEG2, is a cytosolic non-transmembrane PTP encoded by *PTPN9* that is comprised of a PTP domain and a unique lipid-binding domain near the N-terminus. This domain has sequence similarity with yeast phosphatidylinositol transfer protein (Sec14p) and cellular retinaldehyde binding protein, and it targets MEG2 to secretory vesicles through its ability to bind to phosphatidylinositol 3,4,5-triphosphate (PIP3) and phosphatidylserine [106,107]. MEG2 is widely expressed in different tissues, such as brain, leukocytes, and endocrine cells [108,109]. However, the functions of PTP-MEG2 have not been completely characterized yet. Some research has demonstrated that it regulates the growth and expansion of erythroid cells, and it regulates embryonic development [110,111]. Other studies have provided useful progress towards identifying a few substrates of MEG2. MEG2 has been shown to dephosphorylate the nerve growth factor (NGF) receptor TrkA at multiple sites, which resulted in the inhibition of TrkA signaling and NGF-mediated cell differentiation [107]. Additionally, MEG2 has been shown to dephosphorylate and deactivate the insulin receptor in hepatocytes, which downregulates insulin signaling [112]. The use of a substrate-trapping mutant revealed that MEG2 dephosphorylates vascular endothelial growth factor (VEGF) receptor 2, which corresponded with decreased VEGF receptor 2 signaling, as evidenced by the reduced expression levels of the downstream molecules IL-6 and IL-8 [106]. Su et al. [113] were the first to show that STAT3 is yet another substrate of MEG2. Co-immunoprecipitation and glutathione S-transferase (GST) pull-down assays demonstrated that MEG2 directly interacts with STAT3 in vitro, and this interaction was confirmed in in vivo mouse brain tissue and human breast cancer cells. Furthermore, MEG2 dephosphorylated STAT3 at Y705 in a time- and dose-dependent manner, and the inactivation of STAT3 resulted in decreased breast tumor growth [113]. Jin et al. further revealed that the STAT3 inhibitor methyllucidone, a natural compound derived from the fruits of *Lindera erythrocarpa* Makino, inhibited STAT3 activation by upregulating MEG2 expression and, thereby, was effective at inhibiting prostate cancer cell survival and proliferation [114].

8. T-Cell Protein Tyrosine Phosphatase

TC-PTP (encoded by *PTPN2*) is a non-transmembrane protein belonging to the non-receptor, tyrosine-specific subfamily of PTPs, which also includes PTP1B. TC-PTP is comprised of a conserved catalytic domain that shares a high degree (>72%) of sequence and structural homology with the catalytic domain of PTP-1B and a non-catalytic C-terminal domain. TC-PTP has two splice variants that express two isoenzymes: TC45 (45 kDa) possesses a shorter hydrophilic C-terminal domain containing a NLS and TC48 (48 kDa), which has a hydrophobic endoplasmic reticulum targeting sequence within its C-terminal domain [115,116]. TC45 is the major form of TC-PTP in most species; it is primarily found in the nucleus of most cell types, and shuttles between the nucleus and cytoplasm in response to growth factor and cytokine receptor signaling to dephosphorylate distinct substrates [116–118]. Although it is most highly expressed in hematopoietic cells, TC-PTP is ubiquitously expressed in most embryonic and adult tissues [119]. Similar to other PTPs, it regulates major cell processes, such as cell growth and differentiation. For example, insulin, the hormone that maintains glucose homeostasis, triggers the accumulation of TC-PTP in the cytoplasm where it can dephosphorylate the insulin receptor, resulting in the downregulation of insulin signaling [120]. Moreover, TC-PTP has been shown to play unique roles in the immune system [121]. TC-PTP-deficient ($Ptpn2^{-/-}$) mice develop thymus atrophy and succumb to anemia and progressive systemic inflammatory disease within the first 2 weeks of

birth [122]. Additionally, an increase in pro-inflammatory cytokines, such as IFN-γ, IFN-α, or TNF-α, could be found in the 3 days after birth [123]. Older T-cell-specific TC-PTP-deficient (*Ptpn2*$^{-/-}$) mice suffer from spontaneous autoimmunity corresponding with enhanced activation of both CD4 and CD8 T cells in vivo, leading to a reduction in the T-cell receptor (TCR) threshold of activation. In addition, a recent report demonstrated that TC-PTP is a negative regulator of interleukin-7 receptor (IL-7R)-STAT signaling in T-cell progenitors and works as a critical safeguard for efficient T-cell differentiation [124].

TC-PTP has several substrates such as EGF receptor, JAK, and STAT [125,126]. As previously mentioned, TC-PTP is able to play a regulatory role in insulin signaling. TC-PTP-deficient mice (*Ptpn2*$^{+/-}$) displayed decreased gluconeogenesis as a result of the upregulation of STAT3 signaling and insulin-stimulated AKT signaling in the liver [127]. Also, it has been revealed that TC-PTP has some tumor suppressor capabilities. TC-PTP is deleted in a small proportion of human T-cell acute lymphoblastic leukemia, leading to increased JAK/STAT signaling [128,129]. Another study reported a loss of TC-PTP in triple-negative primary breast cancer, and TC-PTP deficiency in human breast cancer cell lines resulted in increased cell proliferation in vitro and xenograft in vivo via reduced SFK (Src family protein tyrosine kinases) and STAT3 signaling [130]. Studies have shown that STAT3 plays a critical role in the development of either chemically or UVB-induced skin cancer by promoting the survival and proliferation of keratinocytes during carcinogenesis [131–137]. Our research group has reported extensively on the role of TC-PTP in the regulation of STAT3 signaling in skin carcinogenesis. Our studies have demonstrated that UVB radiation induces TC-PTP nuclear translocation in mouse keratinocytes, which resulted in a significant decrease in cell proliferation corresponding with a decrease in STAT3 phosphorylation [138,139], suggesting that TC-PTP may serve as a tumor suppressor against UVB-mediated skin carcinogenesis. As previously mentioned, TC-PTP is primarily found in the cell nucleus due to a NLS in the C-terminus. However, we revealed that UVB irradiation triggers phosphorylation at the T179 residue of TC-PTP by AKT, which is required for the nuclear translocation of TC-PTP via 14-3-3σ, a protein critical to signal transduction and cell cycle regulation [139,140]. TC-PTP was also implicated in chemically induced skin carcinogenesis. TC-PTP knockout in mouse epidermis (*K14Cre.Ptpn2*$^{fl/fl}$) led to reduced susceptibility to tumor initiator 7,12-dimethylbenz[a]anthracene (DMBA)-induced apoptosis. Furthermore, TC-PTP deficiency significantly increased epidermal thickness and hyperproliferation following treatment with 12-*O*-tetradecanoylphorbol-13-acetate (TPA), a tumor promoter. During two-stage skin carcinogenesis, the loss of TC-PTP promoted TPA-induced skin carcinogenesis via the upregulation of STAT3 and AKT signaling, whereas the inhibition of STAT3 or AKT recovered the effects of TC-PTP as a tumor suppressor in TC-PTP deficient cell lines (Figure 2) [141]. Our findings implied that TC-PTP is a potential novel target for the prevention of skin cancer through its role in the regulation of STAT3 and AKT signaling.

TC-PTP is the only PTP known to regulate STAT1 other than SHP2. The interaction between STAT1 and TC-PTP may involve associated proteins, such as β-arrestin 1. For instance, during IFN-γ signaling, β-arrestin 1, acting as a scaffold, directly interacts with STAT1 and promotes STAT1 tyrosine dephosphorylation by recruiting TC45 [142]. However, more recent evidence has suggested that β-arrestin 1 does not inhibit STAT1 transcriptional activity nor does it prevent the activation of IFN-γ target genes. Thus, β-arrestin 1 has not been confirmed as a STAT1-interacting protein, and in fact, it has been shown to be negatively regulated in STAT1 signaling [143]. Another interesting study has reported that nuclear TC45 is a major PTP regulator of nuclear STAT1 [144]. It was demonstrated that STAT1 was hyperphosphorylated and activated in TC-PTP-deficient cells. The dephosphorylation of pSTAT1 in TC-PTP deficient mouse fibroblasts was strongly delayed, resulting in the expression of STAT1 target genes. Bussieres-Marmen et al. demonstrated that the knockout of TC-PTP in the intestinal epithelial cells in mice resulted in severe colitis corresponding with increased inflammation and increased cell proliferation via the activation of STAT1 [145]. Interestingly, genetic variations in *PTPN2* have been associated with the chronic inflammatory bowel disease known as Crohn's disease [146].

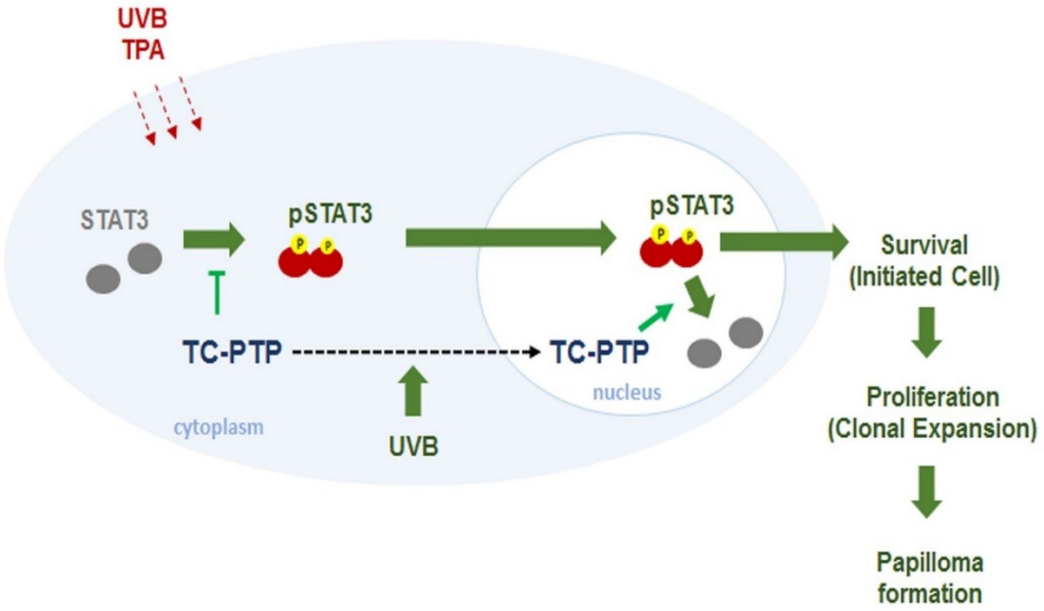

Figure 2. Regulation of STAT3 by T-cell protein tyrosine phosphatase (TC-PTP) in keratinocytes. In response to ultraviolet B (UVB) radiation or 12-*O*-tetradecanoylphorbol-13-acetate (TPA) treatment, TC-PTP dephosphorylates active p(Y)-STAT3 in both the nucleus and cytoplasm of keratinocytes. UVB- or TPA-induced nuclear translocation of TC-PTP by the AKT/14-3-3σ axis can enhance STAT3 dephosphorylation, which can contribute to increased apoptosis and decreased cell proliferation in keratinocytes. This initial cellular response by TC-PTP protects against the development of 7,12-dimethylbenz[a]anthracene (DMBA/TPA)- or UVB-induced skin cancer.

9. Conclusions

The STAT family of transcription factors are vital to the proper functioning of most cell types. They transduce the signals required for the activation of several key cellular processes. A STAT is activated primarily by tyrosine phosphorylation of its C-terminal tail. Tyrosine phosphorylation is a reversible post-translational modification that regulates proteins in multiple ways; however, during carcinogenesis, the rate and duration of tyrosine phosphorylation can become disrupted by genetic mutation or by the inactivation of important phosphotyrosine regulators. STAT3 is constitutively activated in many cancers; therefore, the mechanisms that regulate STAT3 have been, and continue to be, heavily investigated in order to identify newer and more effective targets for anti-cancer therapies. PTPs are the primary enzymes to dephosphorylate phosphotyrosine proteins. The current research has greatly increased our understanding of how STAT3 is regulated by PTP. To date, seven PTPs have been implicated in the regulation of STAT3: PTPRD, PTPRT, PTPRK, SHP1, SHP2, MEG2, and TC-PTP (Figure 3). However, there are 107 members of the PTP family, many with unknown functions. More research is still needed to unravel the many mechanisms by which PTP regulation may contribute to human disease in order to improve upon our current clinical therapies.

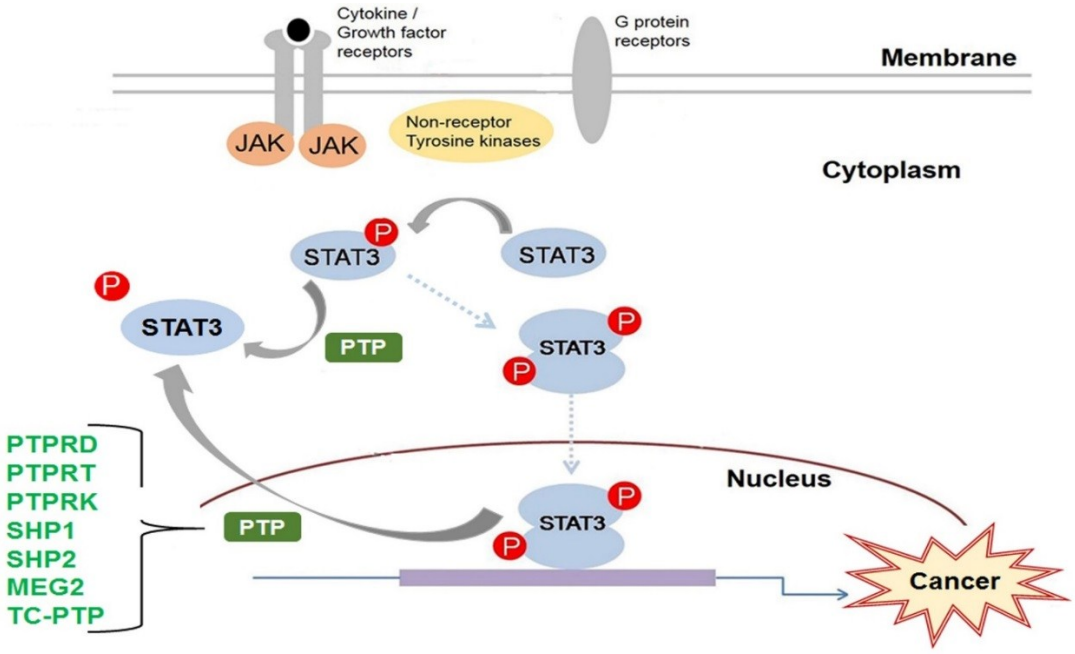

Figure 3. STAT3 dephosphorylation by PTPs in cancer. STAT3 phosphorylation can be initiated by different signaling molecules: cytokine receptors, growth factor receptors, non-receptor tyrosine kinases, or G-protein receptors. Following activation, p(Y)-STAT3 dimerizes and translocates to the nucleus, where it can activate the genes necessary to promote carcinogenesis. The PTPs that have been implicated in the negative regulation of STAT3 in cancer are: PTP receptor-type D (PTPRD), PTP receptor-type T (PTPRT), PTP-receptor-type K (PTPRK), Src homology region 2 (SH-2) domain-containing phosphatase 1 (SHP1), SH-2 domain-containing phosphatase 2 (SHP2), MEG/PTP non-receptor type 9 (PTPN9), and TC-PTP. Dephosphorylation of STAT3 by PTPs can occur in either the cytoplasm or the nucleus. JAK: Janus-activated kinases.

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