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THE IMPACT OF PHOSPHATASES ON PROLIFERATIVE AND SURVIVAL SIGNALING IN CANCER

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Abstract

The dynamic and stringent coordination of kinase and phosphatase activity controls a myriad of physiologic processes. Aberrations that disrupt the balance of this interplay represent the basis of numerous diseases. For a variety of reasons, early work in this area portrayed kinases as the dominant actors in these signaling events with phosphatases playing a secondary role. In oncology, these efforts led to breakthroughs that have dramatically altered the course of certain diseases and directed vast resources toward the development of additional kinase-targeted therapies. Yet, more recent scientific efforts have demonstrated a prominent and sometimes driving role for phosphatases across numerous malignancies. This maturation of the phosphatase field has brought with it the promise of further therapeutic advances in the field of oncology. In this review we discuss the role of phosphatases in the regulation of cellular proliferation and survival signaling using the examples of the MAPK and PI3K/AKT pathways, c-Myc and the apoptosis machinery. Emphasis is placed on instances where these signaling networks are perturbed by dysregulation of specific phosphatases to favor growth and persistence of human cancer.

Introduction

Physiologic signaling relies on the coordinated transduction of messages in a manner that is tightly regulated both in space and time. Thus, the propagation of a signal within the cytoplasmic compartment can have different effects from the same message being transmitted to the nucleus. Likewise, the activation of a signaling cascade in a pulsatile or oscillatory pattern can have divergent phenotypic consequences compared to sustained activity of the same pathway [1]. Among the many mediators of cellular signaling, an immense literature has accumulated about the role of reversible phosphorylation of proteins and other biomolecules in these processes. The opposing actions of kinases and phosphatases act to toggle the activity of biological processes from the “on” to the “off” state in response to upstream stimuli. Moreover, proteins often harbor multiple phosphorylation sites, thereby allowing them to serve as integration nodes for multiple input signals. While the sophistication displayed by this form of cellular communication is both intricate and elegant, it also creates opportunity for dysregulation at a number of steps along

the path from stimulus to biologic output. Such derangements represent the pathophysiologic basis of many disease states.

As major signaling nodes for both extracellular and intracellular stimuli, kinases affect numerous processes that determine cell fate including growth, replication, survival and death. It should, therefore, be of no surprise that many kinases have been identified as drivers of tumorigenesis. In addition to helping to explain the evolution of some cancers, these discoveries have led to novel treatments for patients and have dramatically altered the outlook for several malignancies [2]. Frequently, the targets of these kinases require tight regulation in order to maintain cellular homeostasis. In normal physiology it is the action of phosphatases that opposes kinases to stop or restart a signal or to maintain readiness for future stimuli. Therefore, alterations involving either kinases, phosphatases or both in combination can disrupt this requisite balance in favor of proliferation and survival. It has become increasingly apparent that the balance between kinase and phosphatase activity is tipped in favor of oncogenic signaling outputs across cancer types [3,2]. While our understanding of the contribution of phosphatase signaling to cancer has not yet contributed ammunition to the oncology armamentarium, immense progress has been made toward that end since the first identification of a phosphatase as a tumor suppressor two decades ago [4,5]. In fact, phosphatase modifying agents have advanced to clinical trials in cancer and may provide clinical benefit in the near future [6]. As such, it is essential to maximize our understanding of the contribution of phosphatases to the oncogenic process in order to develop novel therapeutic strategies and to optimize current approaches to targeting these enzymes in cancer.

Phosphatases are categorized according to the amino acids or other molecules that they modify and subcategorized by mechanism of action. Focusing on protein phosphatases, such ontological endeavors give us two major categories: the highly diverse protein tyrosine (Tyr) phosphatases (PTPs) and the protein serine/threonine (Ser/Thr) phosphatases (PSPs; see Figure 1 and Table 1). Analysis of the contribution of each to the overall phospho-proteome has revealed that over 98% of all protein phosphorylation events occur on Ser/Thr residues [7], which makes sense as these modifications often serve to amplify upstream signals. The downstream position of these post-translational modifications (PTMs) places them in close proximity to the final effectors of phenotype, whereas PTPs generally control upstream signals. As a testament to the critical role of both PTPs and PSPs in disease, both families have been the subject of significant drug discovery efforts [8,9]. The goal of this review is to highlight the contribution of phosphatases to the regulation of several major signaling pathways that control cancer cell proliferation and survival.

Introduction to Phosphatases

Protein Tyr Phosphatases (PTPs)

The largest category of phosphatases, the PTP family, contains over 100 members (Reviewed in [10,11]; see Figure 1 and Table 1). “Classical” PTPs with specificity for pTyr alone include nearly 40 members, some being transmembrane-spanning receptor PTPs and others being of the non-receptor type. Additionally included in this family are three classes of dual-specificity phosphatases (DUSPs), which catalyze the removal of phosphate from

pSer/pThr as well as pTyr. Some of these DUSPs have activity toward phospholipids and other biomolecules instead of or in addition to protein phosphatase activity; this subset includes PTEN (phosphatase and tensin homolog deleted on chromosome 10), perhaps the most-studied phosphatase in the field of oncology. Finally, there are the aspartate(Asp)-based and histidine(His)-based PTPs. All but the last two of these groups utilize a cysteine(Cys)-based catalytic site to perform their enzymatic function. PTPs are generally monomeric proteins, with specific domains that determine subcellular localization or perform auto-regulatory functions as well as regions bordering the catalytic site that help to determine substrate specificity.

Importantly, various PTPs demonstrate either inhibitory and/or driving roles in tumorigenesis and tumor persistence. The tumor suppressor PTEN has already been mentioned; additional PTPs exert well-described tumor suppressive functions as well. On the other hand, some PTPs display oncogenic functions in human cancers. For other PTPs, the data is mixed or they exert apparently divergent effects in different tissues or experimental systems. Several PTPs will be discussed in the context of selected pathways that they perturb in cancer. For a more in-depth view of PTPs, interested readers are referred to the following comprehensive reviews [12,10,13].

Protein Ser/Thr Phosphatases (PSPs)

The other major category of protein phosphatases, PSPs, is grouped into three main families- the phosphoprotein phosphatases (PPP), the metal-dependent protein phosphatases (PPM), and the Asp-based phosphatases (FCP/SCP; see Figure 1 and Table 1) [14,12]. These three groups encompass only around 40 distinct catalytic subunits. However, whereas PTPs are generally multi-domain monomeric proteins, some PSPs truly comprise a collection of holoenzymes composed of two or more subunits. For these multimeric PSPs, the diversity of substrate targeting is dramatically increased by their association with different regulatory subunits. For example, while protein phosphatase 2A (PP2A) has only two catalytic isoforms (PP2A-C α and PP2A-C β), by pairing with its two scaffolding (A) subunits and 15 regulatory (B) subunit genes (producing at least 23 isoforms) more than 90 possible trimeric holoenzymes are possible [14]. Likewise, PP1 describes the complex of its catalytic protein (of which there exist three isoforms) with one of numerous regulatory subunits. Therefore, when considering the function of one of these multimeric PSPs in signaling it is critical to think in terms of the specific holoenzyme involved since each heterotrimer is essentially a unique phosphatase as it relates to localization of activity, target specificity and/or phenotypic effects. This combinatorial diversity may help to explain the ten-fold excess of Ser/Thr kinases over PSPs in the genome compared to the near balance in number between protein Tyr kinases and PTPs. It also makes the study of both catalytic and regulatory subunits important to understanding the functional state of these phosphatases in cancer.

The importance of considering all components of a multimeric PSP in cancer may again be best exemplified by trimeric PP2A. Considerable evidence has accumulated regarding altered expression, deletion and/or mutation of various subunits of this phosphatase as well as expression of its endogenous inhibitors across numerous cancer types (Reviewed in [14–16]). Thus, there are many ways in which signaling by this phosphatase are disturbed in

cancer. The multitude of ways in which PP2A components are dysregulated and the overall prevalence of these perturbations in cancer underscore their importance. Yet this complexity likewise increases the difficulty in studying its contributions to the oncogenic process. The aggregate of data published over the past several decades largely implicates PP2A as a tumor suppressor. Yet, some individual PP2A holoenzymes appear to exert oncogenic functions. To further complicate matters, the cellular context required to enable these divergent functions to become manifest are not yet fully understood. This level of detailed understanding of phosphatase activities in cancer will be necessary to properly translate scientific gains in the field to therapeutic benefit for patients with cancer. Other members of the PSP family exhibit either tumor suppressive and/or oncogenic properties as well. Specific examples will be provided in the following sections.

Introduction to Oncogenic Signaling

Hannahan and Weinberg heralded in the 21st century of oncology research by outlining the necessary processes that must be coopted for a cancer to develop [17]. This work and its update [18] laid out the framework with which we think about oncogenic signaling today. The original hallmarks of cancer included sustained proliferative signaling, escape from growth suppression, resistance to cell death, and the induction of angiogenesis, invasion/metastasis and replicative immortality. Cancer-associated genetic alterations trigger signaling aberrations that facilitate the acquisition of one or more of these traits. The work synthesized in the “hallmarks” paper and subsequent advances have revealed a trove of information about the roles of both kinases and phosphatases in cancer development and maintenance. For example, *PTEN* deletion across many cancers [19], SHP2 (*PTPN11*) activating mutation in hematologic and other malignancies [20,21], and a variety of perturbations in components of the PP2A machinery [16,15] provide well-established contributions to tumorigenesis in humans. A full consideration of the influences of phosphatases on all relevant oncogenic pathways is beyond the scope of this article. Thus, for this review we have chosen to frame the discussion around several of the major pathways that contribute to proliferative signaling and to the regulation of apoptosis in cancer. Namely, we will discuss the contribution of phosphatase signaling to the regulation of the phosphatidylinositol 3-kinase (PI3K)/AKT and mitogen-activated protein kinase (MAPK) pathways, c-Myc and the apoptotic machinery. Within this context we will provide examples where altered phosphatase function contributes to the oncogenic process in experimental systems and in human disease.

PI3K/AKT

The PI3K signaling pathway affects many cellular processes including growth, metabolism, proliferation, migration, and apoptosis [22,23]. This kinase directly phosphorylates the lipid molecule phosphatidylinositol-4,5-bisphosphate (PIP₂) to form phosphatidylinositol-3,4,5-trisphosphate (PIP₃; Figure 2). Subsequently, PIP₃ recruits protein kinases such as PDK1 and AKT to the cell membrane by binding to pleckstrin homology (PH) domains that coordinate the protein-lipid interaction [24,25]. One of the major effectors and readouts of activated PI3K signaling is the Ser/Thr kinase AKT, which is activated by phosphorylation at Ser473 by mTORC2 and at Thr308 by PDK1 (reviewed in [26,27]). Other kinases can additionally

phosphorylate AKT. Subsequently, AKT engages several downstream substrates that act as effectors or additional mediators of PI3K signaling. Hyperactivation of this signaling cascade occurs frequently across cancer types, mechanistically through amplification of upstream signals, mutations in oncogenes such as *PIK3CA* among others [28] and loss of tumor suppressive modulators, including several phosphatases, as reviewed herein.

One important PI3K inhibitory tumor suppressor that has already been alluded to is PTEN, whose canonical function is to dephosphorylate PIP3 [29]. By doing so, PTEN counteracts proliferation and cell survival processes activated by PI3K signaling (Figure 1). Two groups independently identified *PTEN* as the tumor suppressor gene located on chromosome 10q23 [4,5], a site known for loss of heterozygosity in many human tumors [30]. Deletion or loss of heterozygosity of *PTEN* occurs in many malignancies including glioma, breast and prostate cancer and hematologic malignancies [19]. Germline mutations in *PTEN* have also been observed in cancer-predisposing syndromes such as Cowden syndrome and are collectively known as PTEN hamartoma tumor syndromes [19,31]. As such, PTEN acts as a driver mutation in the development of cancer through loss of control over PI3K/AKT signaling. However, recent work has shown that even PTEN can perform oncogenic functions, as its deletion or targeted inhibition in B-cell lymphoblastic leukemia/lymphoma (B-ALL) led to regression of disease and enhanced survival in mouse models [32].

Downstream of PI3K, the AKT signaling pathway is inhibited by the PH domain leucine-rich repeat protein phosphatases (PHLPPs), which are part of the PPM subtype of PSPs [33]. PHLPPs were first discovered to dephosphorylate and inactivate AKT directly on its C-terminal Ser473 residue [34]. The two isozymes that comprise PHLPPs are PHLPP1, which modulates AKT2, and PHLPP2, which modulates AKT1 [35]. Other PHLPP substrates include protein kinase C β II [36] and ribosomal protein S6 kinase [37]. Loss or decreased expression of PHLPPs has been observed in tumors of bone, colon and prostate, among others, in line with their tumor suppressive functions [38–43].

Various PP2A holoenzymes regulate the AKT signaling pathway by dephosphorylation at the Thr308 residue, resulting in kinase inactivation [44–48]. The PP2A-B55 α regulatory subunit (encoded by *PPP2R2A*) has been found to directly bind AKT in lymphoid cells [49] whereas the B56 β subunit binds to AKT in adipocytes [50]. The PP2AB56 γ subunit also has been linked to decreased AKT phosphorylation [51]. For B55 α both decreased gene expression and rarely deletion have been shown to occur in acute myeloid leukemia (AML), with the former correlating with reductions in overall survival and increased Thr308 AKT phosphorylation in patients and the latter with sensitivity to AKT-targeted therapy *in vitro* [52,49,53]. Recurrent deletions of *PPP2R2A* also occur in breast, prostate and other cancers [54–56].

Thus, both PTPs and PSPs contribute to the regulation of PI3K/AKT signaling and their dysregulation has a direct role in oncogenesis. Surprisingly, even classical tumor suppressors like PTEN can have context-dependent effects. Continued efforts will be necessary to maximize the potential of targeting these derangements for therapeutic benefit and to develop novel biomarkers to guide treatment decisions.

MAPK signaling

A second major intracellular proliferative and pro-survival signaling pathway involves the proto-oncogene RAS [57]. Physiologic stimuli activate RAS signaling downstream of receptor Tyr kinases (RTKs) and other cell surface molecules (Figure 2). For RTKs, kinase domain phosphorylation produces binding sites for proteins with SRC homology 2 (SH2) domains, with growth factor receptor bound protein 2 (GRB2) being one important SH2-containing adapter. Binding of GRB2 to an RTK activates the guanine nucleotide exchange factor (GEF) activity of son of sevenless protein (SOS). SOS then promotes RAS to exchange GDP for GTP, thereby producing its active state. Once activated, RAS stimulates several effector proteins such as p120 GTPase activating protein (GAP), RalGDS and other GEFs, as well as a number of protein kinases including: PI3K, protein kinase C (PKC), c-Jun NH₂ terminal kinase (JNK), mitogen-activated protein kinase kinase kinase (MEKK), mitogen-activated protein kinase kinase (MEK), and extracellular signal-regulated kinases (ERK1/2) [57]. To extinguish the signal, RAS harbors intrinsic GTP hydrolytic activity that is accelerated by GAPs. Different GEFs and GAPs control RAS activation downstream of various other stimuli. The RAS proteins are additionally regulated by PTMs that contribute to subcellular localization and activity [58]. Depending on cellular context as well as pattern, extent and duration of activation, RAS can trigger a wide variety of responses, ranging from cell death to cell growth and propagation. As with the PI3K pathway, activating mutations in RAS pathway genes (*KRAS*, *NRAS*, *BRAF*, etc.) are common in cancer [28].

Phosphatases provide both positive and negative signals to various components of the MAPK pathway. For one, PHLPP1/2 were found to directly dephosphorylate RAF1 at Ser388, a crucial residue for its activation [59]. Thus, these PSPs negatively regulate both the MAPK and PI3K pathways. Conversely, the PTP SHP2 is a proto-oncogene, with activating mutations enhancing RAS-ERK activity and promoting leukemogenesis [20]. Yet, while its cell intrinsic effects are oncogenic SHP2 appears to additionally have tumor suppressive functions in colitis-associated tumorigenesis [60].

Likewise, there is evidence for both activating as well as inhibitory effects of PP2A-B55α on the RAS signaling pathway through RAF1 and ERK, respectively. First, PP2A-B55α positively regulates this pathway by dephosphorylating Ser259, an inhibitory site on RAF1. Additionally, PP2A-B55α dephosphorylates kinase suppressor of RAS (KSR) at Ser392, within a key 14-3-3 binding site. This dephosphorylation results in the displacement of 14-3-3, subsequent membrane recruitment of KSR and activation of downstream signaling [61,62]. Yet, this same holoenzyme has been implicated in the negative regulation of RAS signaling. Downregulation of B55α has been shown to decrease phosphorylation of ERK1/2 in several different cell types including lung adenocarcinoma and pancreatic ductal carcinoma [63,64]. In these latter systems, PP2A-B55α was not tested as an ERK phosphatase and it remains possible that these effects are indirect.

The RAS signaling pathway is also regulated by the MAPK phosphatases (MKPs), which are among the VH1-like DUSPs [65,66]. Individual MKPs recognize and dephosphorylate various MAPKs. MKP-1 (*DUSP1*) is localized to the nucleus and dephosphorylates ERK, JNK, and p38. MKP-1 has been found to be altered in several cancers [67–74]. In certain

cancer types, its expression is increased in earlier stages and lowered in later stages of the disease. MKP-2 (*DUSP4*) is also localized to the nucleus and dephosphorylates ERK, JNK, and p38 [75,76]. Based on context, there is evidence that MKP-2 expression is anti-tumorigenic in breast, ovarian and non-small cell lung cancers [77–80]. PAC-1 (*DUSP2*) and hVH3 (*DUSP5*) also localize to the nucleus. PAC-1 dephosphorylates ERK and p38 while hVH3 dephosphorylates ERK. PAC-1 is downregulated in several cancers and its overexpression inhibits tumorigenesis; hVH3 is also downregulated in several cancers [81–83]. MKP-3 (*DUSP6*), MKP-4 (*DUSP9*), and *DUSP7* are localized to the cytoplasm. MKP-3 dephosphorylates ERK and MKP-4 dephosphorylates ERK and p38. MKP-5 (*DUSP10*), MKP-7 (*DUSP16*) and hVH5 (*DUSP8*) are localized to both the nucleus and cytoplasm and they dephosphorylate JNK and p38. Thus, MKPs largely function to attenuate the activity of MAPK effectors.

Other phosphatases implicated in control of MAPK signaling include PP2C α (*PPM1A*) and PP2C β (*PPM1B*), which belong to the group of PSPs that require Mn²⁺/Mg²⁺ for their catalytic activity [84–86]. PP2C α and PP2C β regulate the MAPK signaling pathway at multiple levels. PP2C α inhibits JNK signaling by dephosphorylating its upstream activating kinases MKK4 and MKK7. Both PP2C α and PP2C β inhibit p38 by dephosphorylation of two of its upstream activators, MKK3b and MKK6b [87]. Additionally, PP2C α has been found to directly dephosphorylate ERK2 at Thr202, resulting in its inhibition [88]. Both PP2C α and PP2C β are decreased in some cancer types and their overexpression imposes tumor suppressive properties [89–92].

As a phosphorylation signaling cascade, MAPK signaling is normally under the control of phosphatases at multiple levels. The evidence provided above demonstrates several ways in which different phosphatases may have either promoting or inhibitory effects on the output of this pathway, though phosphatases largely serve to dampen proliferative and pro-survival MAPK activity. It will be important to further our understanding of the implications of dysregulated phosphatase activity on the spatiotemporal control of this dynamic pathway. Such efforts may give rise to novel means to modulate MAPK signaling output for therapeutic benefit in cancers.

c-Myc

The transcription factor c-Myc is involved in numerous oncogenic processes, including cell growth, proliferation, metabolism and apoptosis. Expression of the *MYC* gene is increased in many cancers by amplification, translocation, and/or mutation. Under normal conditions, both the gene and its protein product are tightly regulated at the transcriptional, translational and post-translational levels (reviewed in [93]). Its transcript is induced by mitogens and translated in response to growth signals, some of which are mediated by the PI3K and MAPK pathways. In order to enable rapid changes in c-Myc activity, both its mRNA and protein have half-lives between 10-30 minutes in normal cells [94,95]. These short lifespans are the result of stringent regulatory mechanisms that serve to restrict unchecked activity of the proto-oncogene. The disruption of these regulatory mechanisms contributes to tumorigenesis.

At the post-translational level, c-Myc undergoes a series of coordinated phosphorylation/dephosphorylation events, with intervening proline isomerization (Reviewed in [96]; see Figure 3). Phosphorylation of c-Myc at Ser62 by ERK and/or CDKs enhances its transactivation capacity; proline isomerization by Pin1 contributes to full activation of c-Myc [97,98]. The B56 α -containing PP2A holoenzyme dephosphorylates pSer62 on c-Myc that has been secondarily phosphorylated on Tyr58 by GSK-3 β and that for which Pro63 in the *trans* position [99,96]. This dephosphorylation of pTyr58/pSer62 c-Myc to produce the pTyr58 mono-phosphorylated form facilitates its ubiquitination and degradation by the proteasome.

Interestingly, c-Myc binds to the promoter of *PPP2R5D* which encodes for PP2A-B56 δ . This transactivation leads to increased Tyr58 phosphorylation of c-Myc via GSK-3 β activation [100]. This process should function as a negative feedback loop on c-Myc activity. It is therefore important to note that *PPP2R5D* knockout mice spontaneously develop hepatocellular carcinomas with c-Myc Ser62 hyperphosphorylation, confirming one mechanism by which deregulated phosphatase signaling promotes Myc-driven tumorigenesis [101].

Recently, the DUSP Eya1 was found to stabilize c-Myc by dephosphorylating pTyr58 [102]. Interestingly, Eya1 appears to have opposing preference compared to PP2A regarding the isomerization state of c-Myc, as Pin1 inhibited the ability of Eya1 to dephosphorylate pTyr58 [103]. This is in contrast to data showing that Pin1 promotes PP2A dephosphorylation of pSer62 [104]. By preventing the degradation of c-Myc, Eya1 functions as an oncogene; its PTP activity is also oncogenic (Reviewed in [105]). We await a complete understanding of the coordinated interplay among these various PTMs on c-Myc in normal physiology but it is clear that the deregulation of one or more of these processes can tip the balance toward tumor promotion.

Other evidence suggests additional mechanisms by which PP2A and c-Myc interact with one another in cancer. For example, in colorectal cancer, epigenetic silencing of *PPP2R2B* (B55 β) promotes rapamycin resistance in a manner that involves c-Myc activation [106]. Likewise, decreased Axin levels confer increased c-Myc stability in breast cancer by preventing the formation of its destruction complex, which includes PP2A-B56 α [107]. Furthermore, B55 α and c-Myc show a positive correlation in AML patient samples by reverse phase protein array [52]. As an explanation, knockdown of B55 α seems to decrease c-Myc levels due to compensatory increases in the B56 α subunit. Another phosphatase, PTPN2, seems to cooperate in Myc-driven B-cell lymphomas as it is commonly overexpressed in this context and promotes proliferation [108]. However, this PTP is also deleted in T-cell malignancies and breast cancer, where its loss enables elevated JAK/STAT signaling [109–112]. It is possible that ectopic c-Myc expression compensates for the inhibition of STAT signaling by PTPN2 [113], allowing for its oncogenic functions to predominate in c-Myc-driven lymphomagenesis.

In addition to its post-translational regulation by phosphorylation, c-Myc regulation also occurs at the level of translation. Its mRNA is short-lived, as previously mentioned, and like several other oncogenes (Mcl-1, Cyclin D1, etc.) its translation is cap-dependent [114].

Therefore, constitutive activation of cap-dependent translational machinery can augment c-Myc protein translation. Conversely, inhibition of cap-dependent translation can rapidly reduce c-Myc protein abundance. Regulation of cap-dependent translation occurs downstream of both the RAS/ERK and PI3K/AKT pathways, with the former signaling to eIF4E by activating phosphorylation and the latter by inhibitory phosphorylation of 4E-BP1 (Reviewed in [114]). There is *in vitro* evidence that eIF4E and its upstream kinases MNK1/2 are targets for dephosphorylation by PP2A [115]. The activity of PP2A also serves to reduce 4E-BP1 phosphorylation but this probably occurs indirectly through inhibition of the PI3K/AKT pathway [116]. Another PSP, PPM1G, dephosphorylates 4E-BP1 to inhibit cap-dependent translation [117]. Interestingly, PPM1G is itself a phosphoprotein that undergoes activating phosphorylation by ATM and inhibitory phosphorylation downstream of PI3K/AKT [118,119]. Thus, loss of ATM and/or increased activity of the PI3K pathway, both of which are common in cancers, will diminish PPM1G activity and promote cap-dependent translation. PHLPPs, negative feedback regulators of AKT already mentioned above as being lost or depleted in various malignancies, block cap-dependent translation by inhibitory dephosphorylation of S6K1 [37,120]. Thus, the activity of several tumor suppressive phosphatases serves to decrease translation of *MYC* and other cap-dependent oncogenes and the loss of such phosphatase activity is relevant to human cancer.

From direct protein dephosphorylation to alter its stability and activity to regulation of pathways that control its synthesis, phosphatases contribute heavily to the tight regulation of c-Myc activity. Furthermore, c-Myc itself drives expression of a negative feedback regulatory B subunit of PP2A. This stringent phosphatase-mediated regulation is lost in many cancers and, moreover, oncogenic phosphatase activity additionally cooperates with c-Myc or enhances its function in some cancer types. As c-Myc has proven difficult to target pharmacologically, phosphatase targeting agents have great potential to provide new means to affect this critical oncogene.

The Apoptosis Cascade

Among the aforementioned hallmarks of cancer is the evasion of apoptosis, an evolutionarily conserved process of programmed cell death. Its two major branches, extrinsic and intrinsic, allow for the activation of this process both by external signaling to death receptors and by altering the rheostat of Bcl-2 family members in response to various cellular stresses (reviewed in [121,122]). Furthermore, the extrinsic pathway can amplify the activity of the intrinsic pathway, which is necessary for robust apoptosis in some cell types. The extrinsic pathway of apoptosis begins with interaction between a death receptor and its ligand, which activates a signaling cascade to produce the death-inducing signaling complex (DISC); its initial caspase effector is caspase-8. The intrinsic, or mitochondrial, pathway commences with oligomerization of Bax and/or Bak to cause mitochondrial outer membrane permeabilization (MOMP); this pore formation allows for the release of cytochrome c and other pro-apoptotic factors from the mitochondria. Cytochrome c pairs with apoptotic peptidase activating factor-1 (APAF-1) and dATP to activate pro-caspase-9, together termed the apoptosome. Whether initiated by caspase-8 or caspase-9, the two apoptotic pathways converge on activation of caspase-3 and caspase-7 as the final executioners (see Figure 4).

Though these caspases share some common substrates, they appear to perform distinct roles in the apoptotic process as well [123].

Along with both using the same effector caspases, another shared feature of the two apoptotic pathways is their regulation by Bcl-2 family members. For the intrinsic pathway, the interplay between these proteins governs the decision to undergo apoptosis; for the extrinsic pathway, the truncation of Bid by caspase-8 allows for crosstalk with the intrinsic pathway. The apoptosis-governing Bcl-2 proteins share regions of homology that, along with their function in promoting or inhibiting apoptosis, allow them to be separated into three groups: the anti-apoptotic proteins, the Bcl-2 homology 3 (BH3)-only members and the multi-domain pro-apoptotic forms Bax and Bak (reviewed in [124]). The anti-apoptotic Bcl-2 family members function by sequestering their pro-apoptotic homologs. This group includes the founding member Bcl-2, as well as Bcl-A1, Bcl-w, Bcl-xL and Mcl-1. The BH3-only proteins include Bad, Beclin-1, Bid, Bim, Blk, Bmf, Hrk, Noxa, and Puma. This group can be further divided into; 1) direct activators, those proteins that interact directly with Bax and/or Bak to induce their oligomerization in the mitochondrial outer membrane and 2) sensitizers, those members that bind to anti-apoptotic Bcl-2 family members and thereby free up their direct activator homologs to activate Bax/Bak (Figure 4). Other models exist that introduce subtle distinctions about the modes of interaction between Bcl-2 family members in controlling apoptosis based on extensive experimental data [125]. Basically, the stoichiometric ratio between pro- and anti-apoptotic proteins determines cell fate. However, the localization and interaction between Bcl-2 family members is additionally modulated by PTMs. To add an added layer of complexity, several Bcl-2 family members have splice variants with distinct activities to their full-length isoforms and some perform functions in addition to their canonical roles in apoptosis regulation.

While changes in susceptibility of cancer cells to apoptosis have been attributed to knockdown/knockout or overexpression of a number of phosphatases, for this section we will focus on phosphatase activities that directly regulate components of either the intrinsic or extrinsic pathways of apoptosis.

Regulation of the Intrinsic Apoptotic Pathway by Phosphatase Signaling

It should come as no surprise that phosphorylation controls the activity of apoptosome complex proteins, as apoptosome-mediated caspase activation represents a point of no return. For example, APAF-1 undergoes inhibitory phosphorylation by 90-kDa ribosomal S6 kinase [126]. Additionally, caspase-9 is heavily phosphorylated, reportedly at 11 sites by as many as nine different kinases [127]. As is a common theme among apoptosis-regulating proteins these phosphorylation events decrease apoptosis induction, although there is one disputed site of supposed pro-apoptotic phosphorylation on caspase-9 (Tyr153) [127,128]. Despite the abundance of literature on phosphorylation of these critical apoptotic mediators, there is a lack of evidence about the regulation of these anti-apoptotic PTMs by phosphatase signaling. Yet, the contribution of phosphatases is likely important. The phosphatase inhibitor okadaic acid (OA) was shown to enhance phosphorylation of Thr125 on caspase-9 [129], while a later report confirmed that PP1 α can dephosphorylate this site to promote apoptosis [130].

Members of the Bcl-2 family display diverse mechanisms of regulation, with some primarily under transcriptional control and others more tightly controlled at the level of translation or by PTMs including phosphorylation and ubiquitination. These post-translational changes control the stability, subcellular localization and/or binding characteristics of each protein.

Among the pro-apoptotic BH3-only proteins, several have been shown to be regulated by phosphorylation. For example, Noxa phosphorylation by CDK5 inhibits its function by partially masking its BH3 domain [131,132]. Similarly, the BH3-only protein Bmf additionally undergoes anti-apoptotic phosphorylation by ERK2 [133]. In a variation on the theme, phosphorylation of Bim and Puma target them for ubiquitination and subsequent proteasomal degradation [134,135]. Conversely, the pro-apoptotic activity of Bik is reportedly enhanced by phosphorylation [136,137]. The counteracting phosphatases for these BH3-only proteins are not yet known. However, a number of phosphatases have been implicated in dephosphorylation of the BH3-only protein Bad, which is phosphorylated downstream of growth factor and other proliferative and survival signals [138]. The implicated phosphatases include PP2A [139], PP2C β [140], PP1 [141], and PP2B [142]. While Bad contains a number of phosphorylation sites [143], in all reported cases dephosphorylation promotes mitochondrial localization and/or pro-apoptotic activity.

A multitude of studies have described phosphorylation of anti-apoptotic Bcl-2 in various contexts, much of which indicates that phosphorylation at Ser70 enhances its anti-apoptotic function (Reviewed in [144]). Dephosphorylation of Bcl-2 Ser70 has been shown to reduce its anti-apoptotic function [145,146]. However, competing data shows that expression of a Ser70Asp Bcl-2 phospho-mimetic promotes pro-apoptotic Bax translocation to the mitochondria in neuronal apoptosis [147]. Others have found that Bcl-2 multi-site phosphorylation frees Beclin-1 to promote autophagy [148]. Additional work using phospho-mimetics and phospho-null mutations have produced conflicting results in different contexts (reviewed in [144]).

Many early studies on Bcl-2 family phosphorylation were performed in the context of microtubule-targeting agent (MTA) treatment, which induces multi-site phosphorylation of Bcl-2, Bcl-xL and Mcl-1 [149–153]. For Mcl-1, this leads to degradation. For Bcl-2 and Bcl-xL, this (poly)-phosphorylation seems to reduce their ability to sequester pro-apoptotic BH3-only proteins, though to what extent remains under debate [154]. Interestingly, Bcl-2 and Bcl-xL are also normally phosphorylated during mitosis, the exact function of which remains to be clarified [155]. There is also some ambiguity in the literature, as not all phosphorylation sites were interrogated in the different studies. In contrast, biophysical characterization shows that Bcl-2 Ser70 mono-phosphorylation increases binding affinity for Bak and Bim, thereby making it a more potent inhibitor of apoptosis [156]. To complicate matters, this study also found that both Glu and Ala mutations at all known Bcl-2 phosphorylation sites showed increased affinity for Bak. The Ser70 mutants also showed increased accessibility to proteolysis. It was hypothesized that these phosphorylation events may expose the flexible loop of Bcl-2. It has not been tested whether Bcl-xL may undergo a similar conformational change upon phosphorylation. If so, the conclusions generated by “phospho-null” Ala mutations may need to be revisited [157–159,151]. Some work has suggested that Ser62-phosphorylated Bcl-xL does have reduced ability to sequester Bax

[151]. Clearly, there is further work to be done to clarify the effects of these several phosphorylation events on Bcl-2/Bcl-xL. For many years, PP2A was the only phosphatase known to dephosphorylate these Bcl-2 family members, with both PP2A-B56 α and -B56 δ being implicated in Bcl-2 dephosphorylation [145,146,158,160]. A related PSP, PP6, was recently shown to act as a Bcl-xL phosphatase in a murine B cell line to prevent its proteasomal degradation [161]. Moreover, both Bcl-xL and Bcl-w interact with PP1 α but it is unclear whether or not these two anti-apoptotic proteins are PP1 substrates [162].

In addition to its activity towards anti-apoptotic Bcl-2 family members, PP2A has been implicated in dephosphorylating pro-apoptotic proteins Bad (as previously mentioned) and Bax to promote apoptosis [139,163]. Furthermore, PP2A can dephosphorylate Bim in a manner that prevents its proteasomal degradation [164]. The indirect PP2A activator FTY720 was also shown to increase Bim as well as truncated Bid (t-Bid) levels in CML cells [165]. Ceramide, another indirect PP2A activator, was also shown to increase t-Bid levels [166]. However, the exact relationship between PP2A and the regulation of Bid remains unclear. Conversely, PP2A has also been implicated in dephosphorylation of Bcl-xL at Ser62, which was shown to enhance its anti-apoptotic function [158]. In most of these cases, the specific B subunit that coordinates target specificity has not been identified. As PP2A has emerged as a promising therapeutic target, the potential for synergistic or inhibitory effects of combinatorial strategies employing PP2A-modulating agents with MTAs and other chemotherapies must be carefully considered.

Anti-apoptotic Mcl-1 is somewhat unique among Bcl-2 family members in its larger size and presence of additional regulatory motifs. A number of kinases, including GSK-3 β and ERK, CDK-1, can phosphorylate Mcl-1 (Reviewed in [167]). Mcl-1 phosphorylation at Ser64 enhances its anti-apoptotic activity [168], whereas Ser159 phosphorylation by GSK-3 promotes its proteasomal degradation [169,170]. These examples highlight the possible pro- and anti-apoptotic effect of phosphorylation on Mcl-1. There are additional phosphorylation sites on Mcl-1 to which varied functions are attributed (reviewed in [167,171]). As for the role of phosphatases in Mcl-1 regulation, two indirectly-acting PP2A activating drugs, OP449 and FTY720, were shown to decrease Mcl-1 levels in CLL cells [172,173]. In lung cancer cells, PP2A knockdown or OA treatment increased Mcl-1 levels in multiple contexts [174,115]. These pharmacologic data suggest that PP2A may promote Mcl-1 degradation. This possible mechanism has yet to be definitively addressed. However, the Ruvolo lab demonstrated that C6-ceramide, whose effects include PP2A activation, led to JNK-dependent increase in Mcl-1 phosphorylation at an undetermined site [175]. Thus, the effect of PP2A on Mcl-1 phosphorylation may be indirect. As Bcl-xL phosphorylation was also increased in these experiments, it may be that ceramide produces a mitotic arrest that leads to subsequent Bcl-2 family member PTMs [176]. However, a different study showed that both pharmacologic and genetic PP2A inhibition led to increased Mcl-1 phosphorylation and subsequent decrease in Mcl-1 protein levels in a Burkitt lymphoma cell line [160]. It will be essential to further understand the role of PP2A and other phosphatases in the control of Mcl-1, as it is an important mediator of cancer cell survival and chemoresistance.

Regulation of the Extrinsic Apoptotic Pathway by Phosphatase Signaling

Phosphorylation of Bid on several Ser/Thr residues reduces its cleavage by caspase-8 downstream of Fas activation [177]. This phosphorylation appears to uncouple or at least delay death receptor activation from commitment to apoptosis [178]. However, we are unaware of any data implicating a specific phosphatase to counter this phosphorylation event, though it was speculated that PP2A may be involved [177]. It has been shown that re-expression of PTEN sensitizes LnCap cells to the extrinsic pathway and increases Bid cleavage but this sensitization occurs at the level of increased caspase-8 cleavage [179]. This PTP more likely enhances apoptosis through its effects on the PI3K/AKT pathway.

Among PTPs, recent work found that SHP-1 dephosphorylates Tyr238 and Tyr291 on Fas to promote apoptosis [180]. In addition, SHP-1 dephosphorylates caspase-8, again with a pro-apoptotic effect [181]. However, there is competing data on whether SHP-1 promotes or inhibits extrinsic apoptosis (Reviewed in [182]). Its effects on cell death may be context or cell type dependent. Fas-associated phosphatase-1 (FAP-1, encoded by the *PTPN13* gene), another PTP, inhibits Fas-activation of the extrinsic apoptotic pathway, potentially by dephosphorylation of Fas (as demonstrated *in vitro* [183]) or by preventing surface expression of Fas [184]. However, among other reported functions (dephosphorylation of IRS-1, HER-2, STAT4, etc.) this non-receptor PTP also dephosphorylates I κ B α , which serves to attenuate NF- κ B activation (reviewed in [185]). Interestingly, FAP-1 is a transcriptional target of NF- κ B, meaning that FAP-1 may serve to block Fas-mediated apoptosis in cancers with constitutive NF- κ B activity [186,187]. Thus, FAP-1 exhibits characteristics of both an oncogene and a tumor suppressor but its phosphatase activity appears to function as the latter. Finally, the DUSP MKP-1 is overexpressed in prostate cancer where it inhibits Fas ligand (FasL)-induced apoptosis [188]. This phosphatase preferentially targets p38 and JNK. These examples show that PTPs exert both inhibitory and activating effects on extrinsic apoptosis.

Yet, not only PTPs contribute to the regulation of extrinsic apoptosis. In fact, pharmacologic or genetic inhibition of PP2A reduced Fas-induced apoptosis [189]. Furthermore, FasL-induced apoptosis of neutrophils correlates with a rapid induction of PP2A activity and PP2A can dephosphorylate caspase-3 *in vitro*, a pro-apoptotic event [190]. In this way and with its effects on Bcl-2 family members, PP2A may serve to cross-activate the intrinsic pathway to help amplify extrinsic death signals. However, some inhibitor experiments suggest that PP1 plays a more important role than PP2A in controlling the extrinsic pathway [191].

In summary, two general patterns emerge from existing data on phosphatase signaling in the control of apoptosis. First, dephosphorylation more commonly exerts a pro-apoptotic function, which is not surprising. Second, current data suggests that PTPs have a greater role in regulating the extrinsic apoptosis pathway, whereas PSPs exert more regulatory control over Bcl-2 family members. As with any biological system these rules have exceptions, some of which are highlighted above.

Targeting Phosphatases in Cancer

Given the contribution of aberrant phosphatase signaling to oncogenic pathways, including those examples detailed herein, there exists strong rationale to seek therapeutic benefit via judicious targeting of these enzymes in appropriate contexts, especially as part of combination therapies. For tumor suppressive phosphatases that are lost in cancer, direct targeting is not an option. However, such aberrations may engender sensitivity to other targeted agents. For example, PTEN deficiency may determine susceptibility to certain therapeutics (reviewed in [192]). In addition, some phosphatases are inhibited by non-deletional mechanisms. In this context, as with PP2A, activating the phosphatase activity has been demonstrated to be a promising therapeutic approach [193–195]. In other circumstances innovative approaches to restoring phosphatase activity may be required.

Targeting oncogenic phosphatases may be a more straight-forward endeavor. Several inhibitors of oncogenic PTPs are in various stages of development, as outlined in several recent reviews [8,196,185]. For PP2A, in addition to activation strategies researchers are investigating its inhibition for treatment of various cancers [197]. These opposing approaches each have merit in that different PP2A holoenzymes possess either tumor suppressive or oncogenic functions. Time will tell whether one or both of these approaches to targeting PP2A will provide clinical benefit. Moreover, selectively targeting individual PP2A holoenzymes may be necessary to maximize the potential of this therapeutic strategy. There are a number of recent reviews that discuss the therapeutic targeting of PP2A and other PSPs in cancer [9,198,15,199–201,197,202].

One theme that recurs throughout this review is the potential context-dependence and/or holoenzyme specificity to the tumorigenic or tumor suppressive roles of various phosphatases. This complexity and the apparently contradictory roles of some phosphatases render their eventual therapeutic targeting even more challenging. As such, many levels of scientific inquiry are still needed to determine the best applications of phosphatase-targeting agents in cancer [203]. Such efforts represent the next step toward the ultimate goal of turning knowledge of phosphatase functions in cancer into cures and prolonged life for cancer patients.

Conclusions and Future Perspectives

In this review, we have illustrated multi-faceted control over several key oncogenic growth and survival pathways by phosphatases. Additionally, we have outlined examples where deregulation of phosphatase signaling contributes to cancer development and where it appears to cooperate with additional oncogenic aberrations to promote tumorigenesis. Moreover, some phosphatases exert both oncogenic and tumor suppressive functions, likely depending on cellular context. While the majority of data agrees with the long-standing concept that phosphatases act as an “off” switch for kinase-activated oncogenic activity, important examples are given wherein phosphatase activity drives proliferation and/or survival. With the wealth of information that has emerged about phosphatase-mediated control of oncogenic processes, we are approaching a point where these gains will soon translate to novel therapies for cancer and other diseases. Yet, our expanded knowledge has

also unveiled potential complications in targeting phosphatases in cancer. For one, are enzymes with both oncogenic and tumor suppressive functions off limits as drug targets? For multimeric phosphatases, can we target individual holoenzymes to attain specificity for desired substrates? Does loss or mutation of specific subunits alter sensitivity to phosphatase-targeted or other therapies? What therapeutic strategies will show combinatorial effects with phosphatase inhibitors/activators and which ones may be antagonistic? As the field progresses, we will continue to address these questions. In doing so the potential to derive therapeutic gain from targeting phosphatases will likely come to fruition.

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Fig. 1. Schematic representation of selected serine/threonine phosphatases, dual specificity (DUSP) phosphatases, non-receptor protein tyrosine phosphatases, and receptor tyrosine phosphatases. Several, but not all, important domains are depicted (see the legend at the bottom of the figure). For multi-subunit phosphatases, only the catalytic subunit is depicted. Among PSPs, note the difference in complexity between the catalytic subunits of multimeric PP2A and PP2B and the monomeric PHLPPs. CaM, calmodulin; PDZ, post synaptic density protein 95, discs large homolog 1, zonula occludens-1.

Fig. 2.

Control of the PI3K and RAS signaling pathways by phosphatase signaling. Phosphatases that target components of one or both pathways are shown in violet. Arrows denote activating whereas bar-headed lines denote inhibitory effects. For simplicity, the intervening steps between stimulation of the various receptor types and PI3K/RAS pathway activation are not depicted. See text for further details. GPCR, G protein-coupled receptor; RTK, receptor tyrosine kinase.

Fig. 3. c-Myc regulation by post-translation modifications. Kinases are shown in green, phosphatases in magenta and the proline isomerase Pin1 is shown in lavender. The c-Myc *trans/cis* isomerization status at Pro63 is denoted by P63_{t/c}; the two critical phosphorylation sites described in the text are denoted as T(Thr)58 and S(Ser)62. Dephosphorylation of GSK-3β by PP2A-B56δ activates the kinase to phosphorylate c-Myc at Thr58. Note the bolder transcriptional activation arrow associated with the doubly phosphorylated c-Myc, as this isoform is thought to have higher transcriptional activity. See text for further details.

Fig. 4.

Apoptosis signaling pathway and its control by phosphorylation. Phosphorylation events that promote apoptosis are highlighted in green while those that inhibit apoptosis are highlighted in red. Propagation of the apoptotic signal is denoted with an arrow. Inhibitory interactions are denoted with bar-headed lines (for example, t-Bid/BIM/PUMA inhibit the anti-apoptotic Bcl-2 proteins whereas the anti-apoptotic Bcl-2 proteins inhibit Bax/Bak activation). The dotted rectangles represent groups of Bcl-2 family members with differential binding partners (i.e., Noxa preferentially binds to A1 and Mcl-1, whereas Bad/Bik/Bmf/Hrk bind more strongly to Bcl-2/Bcl-w/Bcl-xL). See text for further details on the involved kinases and phosphatases.

Table 1

Overview of protein phosphatases with annotation of reported tumor suppressive and/or oncogenic functions. Adapted from [14,12].

Phosphatase Type	Catalytic Mechanism/ Structural Division	Class	Subclass	Group	N	Substrates	Tumor Suppressive Phosphatases	Oncogenic/Pro-Tumorigenic Phosphatases	Phosphatases with Dual/Ambiguous Roles in Cancer
PTP	Cys-Based	Class I	I: Classical	Receptor	20	pTyr, PIPs	PTPRB [204,205], PTPRD[14], PTPRR[206,207], PTPRS [208,209], PTPRT[14,210]	PTPRE[211,212], PTPRH[213,214], PTPRN[215], PTPRN2[216,217]	PTPRA/F/G[14], PTPRJ[13,14,218], PTPRK[219–221], PTPRM[222–226], PTPRO[13,14], PTPRZ[13]
				Non-receptor	17	pTyr	PTPN6(SHP-1)[14], PTPN9[227], PTPNI2[228,229] PTPNI4[230,231]	PTPN11(SHP2) [13,20,21], PTPN21[232]	PTPN1[233], PTPN2 [108–112], PTPN3[13,14], PTPN7[234,235], PTPNI3(FAP-1)[183,184,186,187,236, 237], PTPN22[238,239]
		Class II: LMW-PTP			2	pTyr or pSer			ACPI (LMW -PTP) [255]
	Asp-Based	Class III: CDC25			3	pTyr, pThr		CDC25A-C[256,257]	
		PGMs			4	pTyr, pSer		EYA1 -4[105]	
PSP	His-Based	ACPs			2	pTyr, pSer, pThr, Other	ACPP[14]	UBASH3B[258]	
	PPP				3	pSer, pThr	PP2A[14–16]	PP5[259]	PPI [130,141,260]
	PPM				13	pSer, pThr	ILKAP [261,262], PDP1[263,264], PP2CB[91,265,266], PHLPP1/2[9,14]	PPMID(Wip1)[9]	PP2Ca[89,90,92,265,267,268], PPM1E[269,270], PPM1H[271–274]
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Phosphatase Type	Catalytic Mechanism/ Structural Division	Class	Subclass	Group	N	Substrates	Tumor Suppressive Phosphatases	Oncogenic/Pro-Tumorigenic Phosphatases	Phosphatases with Dual/Ambiguous Roles in Cancer
	SCP/FCP				7	pSer, pThr			SCP[275,276]