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The regulatory roles of phosphatases in cancer

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Abstract

The relevance of potentially reversible post-translational modifications required for controlling cellular processes in cancer is one of the most thriving arenas of cellular and molecular biology. Any alteration in the balanced equilibrium between kinases and phosphatases may result in development and progression of various diseases including different types of cancer, though phosphatases are relatively under-studied. Loss of phosphatases such as PTEN (phosphatase and tensin homologue deleted on chromosome 10), a known tumor suppressor, across tumor types lends credence to the development of PI3-kinase inhibitors alongside use of the phosphatase's expression as a biomarker, though phase 3 trial data are lacking. In this review, we give an updated report on phosphatase dysregulation linked to organ-specific malignancies.

A. Gastrointestinal malignancies

1. Esophageal cancer

Loss of *PTEN* expression in esophageal cancer is frequent, amongst other genes alterations characterizing this disease. Zhou *et al*. found that over-expression of *PTEN* suppresses growth and induces apoptosis in esophageal cancer cell lines, through down-regulation of *BCL2* resulting in changes in cell cycle progression. Moreover they have shown that *PTEN* gene therapy reduces tumour size *in vivo*, suggesting *PTEN* as an important biological marker (1). In addition, Hou *et al*. investigated the relationship of *PTEN* status and cell sensitivity to chemotherapeutic drugs *in vivo*. ESCC cells transfected with or without the wild type (wt) *PTEN* were inoculated subcutaneously into nude mice. Both wt *PTEN* and cisplatin could inhibit tumour growth and induce cell apoptosis. Cisplatin had the strongest inhibitory effects on tumours produced by cells transfected with wt *PTEN*, indicating that *PTEN* can increase the *in vivo* sensitivity of ESCC cells to cisplatin (2). As further evidence of the importance of *PTEN* in esophageal carcinogenesis, Juan Man *et al.* have recently found a strong association of genetic polymorphisms in *PTEN* with high risk of ESCC (3).

In another study, immunohistochemistry (IHC) of 100 patient's tumours with revealed that CDC25A and CDC25B phosphatases are strongly expressed in the cytoplasm of cancer cells (4). Furthermore, due to the role of CDC25B in cell growth, Dong *et al*. examined the levels of CDC25B antibodies (ab's) in sera from 134 esophageal squamous cell carcinoma patients and determined that they are higher compared to healthy subjects. Detection of CDC25B ab's in combination with traditional tumour markers (i.e. CEA, SCC-Ag, CYFRA21-1) resulted in an increased sensitivity of detection, with 64.2% of patients testing positive for at least one of these markers. Moreover, high levels of CDC25B ab's in sera were significantly associated with poor survival in advanced ESCC suggesting that they may have a clinical utility in ESCC screening and diagnosis (5).

Cao *et al*. investigated the role of *PTPN12* in ESCC and showed that PTPN12 protein expression is higher in normal para-cancerous tissues than in 20 ESCC tissues. By performing IHC, high and low expression of PTPN12 was found in 62.1% and 37.9% of ESCCs, respectively. Moreover they demonstrated that patients with completely resected ESCC and tumours with high PTPN12 expression tumour had favorable survival compared to that of patients with low PTPN12, therefore proposing that PTPN12 can be used as an independent predictor of patient survival (6).

Yan-Jie You *et al*. evaluated the methylation levels of protein tyrosine phosphatase receptor type O (*PTPRO*) promoter as a potential biomarker in ESCC. Their analysis revealed hypermethylated PTPRO promoter status in 27 (75%) out of 36 primary tumours. No methylated *PTPRO* was observed in normal peripheral blood samples from 10 healthy individuals. In addition, in *PTPRO*-silenced cell lines, expression was dramatically restored by

treatment with the demethylating agent 5-azadC, confirming that DNA methylation is a mechanism regulating *PTPRO* expression and that aberrant methylation of the *PTPRO* promoter is directly responsible for transcriptional inactivation of its expression in ESCC cell lines. These findings suggest that *PTPRO* is a common target for epigenetic silencing via methylation in ESCC, and that its methylation may be involved in esophageal cancer tumourigenesis (7). Moreover, Motiwala *et al*. examined the levels of *PTPRO* methylation in blood cells, since the presence of detectable methylated promoter DNA in blood cells has been reported to indicate the presence of circulating cancer cells during the process of distant metastasis. Interestingly, *PTPRO* methylation occurred only in B-cell population of a subset of patients with chronic lymphocytic leukemia (CLL), but not in normal B or T lymphocytes, indicating that methylated *PTPRO* in blood cells is cancer-specific (8). Finally, a high frequency of *PTPRO* hypermethylation in primary tumours significantly correlated with tumour stage, indicating that *PTPRO* methylation may be involved also in invasion of ESCC (7).

2. Gastric Cancer

Insertion of cagA-protein from *H. pylori* into the gastric epithelial cells specifically binds and activates PTPN11 oncoprotein (9, 10). Activated PTPN11 induces cell growth and motility (11), while deregulation of PTPN11 by cagA induces abnormal proliferation and migration of gastric epithelial cells that leads to gastric carcinogenesis (12). Several studies detected aberrant DNA methylation of *PTPN6* gene in gastric carcinomas. *H. pylori* infection led to a decrease in the methylation levels in *PTPN6 (13)*, inconsistent with a previous report (14). Yang *et al.* reported that *PTPN1* gene was amplified in gastric cancer tissues (15). With regards to the clinicopathologic characteristics, PTPN1 was associated with tumour metastasis and tumour-node-metastasis stage, implicating its involvement in the development of gastric cancer (16). As suggested, PTPN1 inhibitors may also be useful in the treatment of gastric cancer (17).

PTPN3 and *PTPN4* are two closely-related non-receptor tyrosine phosphatases that are expressed in human gastric cancer cells and tissue specimens (18). PTPN3 dephosphorylates and cooperates with p38γ, to form a complex that may increase Ras oncogenesis through PDZ-mediated direct binding (19). The phosphatase activity of PTPN4 has been implicated in the regulation of cytoskeletal events (20). Overexpression of PTPN4 in COS-7 cells decreased colony formation, inhibited cell growth and decreased saturation density of these cells (21).

Wu and colleagues applied a RT-PCR-based protein-tyrosine phosphatase (PTP) profiling approach to study PTP expression in human gastric cancer samples, and identified sixteen PTPs in the cancer tissues; only six of them (PTPN4, PTPRB, PTPRH, PTPRJ, PRPRN and PTPRZ) were expressed in gastric cancer tissue (22), while PTPRA expression was significantly high in cancer tissues. The role of protein tyrosine phosphatase receptor type

A (PTPRA) in gastric cancer might be linked to its biological role in integrin signaling, cell adhesion and activating the SRC family tyrosine kinases (23-25). Reduced protein tyrosine phosphatase receptor type G (PTPRG) expression was detected by IHC in gastric tumour (22) indicating it might be a tumour suppressor gene. In addition, differences in DNA methylation of *PTPRG* genes between primary tumour and metastatic lymph nodes of gastric cancer was also observed (26). Until now, the detailed mechanisms underlying PTPRG-mediated cell signaling are undescribed.

In a mutational analysis study conducted by Wang *et al*., protein tyrosine phosphatase receptor type *T* (*PTPRT*) was the most common mutated gene (27). Lee et *al*., also detected a splice-site mutation in *PTPRT* gene in 1 of 48 gastric carcinomas and suggested that *PTPRT* phosphatase domain mutation may not play arole in the development of human cancers (28).

Finally, various reports have demonstrated over-expression of protein tyrosine phosphatase receptor type H (PTPRH) (29), DUSP1 (30) and phosphatase of regenerating liver (PRL-3) (31-35) in human gastric cancer, while Ooki *et al*., (36) showed that PRL-3 genomic amplification was associated with advanced stage.

3. Colorectal Cancer

A systemic mutational analysis of the tyrosine phosphatome in human CRC has identified 83 somatic mutations in *PTPRF, PTPRG, PTPRT, PTPN3, PTPN13* and *PTPN14* genes (27). Similarly, frameshift mutations have been depicted in *PTPRA, PTPRS, PTPN5, PTPN13, PTPN21* and *PTPN23* (37), while hypermethylation of *PTPRO* was showing microsatellite instability colorectal tumours (38).

PTPN13 was shown to interact with the cytosolic domain of Fas (39), while Miyazaki *et al*. reported over-expression of PTPN13 enhances sensitivity to Fas-mediated apoptosis (40). However, Yao *et al.* demonstrated that expression of PTPN13 in more than 70% of colon cancers, was related to resistance against Fas-mediated apoptosis *in vivo* and *in vitro (41)*. These contradictory reports reveal that PTPN13 may possess dual role in colon carcinoma, either as an oncogene or as a tumour suppressor depending on the cellular context in which it is studied.

Lassmann et *al*. evaluated distinct genomic DNA alterations using array comparative genomic hybridization and identified DNA amplification of *PTPN1* in 22% of the colorectal cancer cases, with the highest percentage in changes in chromosomal-positive tumours (42). PTPN1 has been responsible for the activation and elevation of Src kinase activity in six human epithelial colon cancer cell lines (43).

Enhanced Src activity mediates signals and directs downstream activation of the JAK-STAT pathway. Signal transducer and activator of transcription 3 (STAT3) has been shown to be activated in colon tumours and cell lines (44, 45). Protein tyrosine phosphatase receptor-

type T (PTPRT) and protein tyrosine phosphatase receptor-type D (PTPRD) were shown to be able to regulate STAT3 (46, 47). As aforementioned, the mutation screen established that *PTPRT* was the most frequently mutated PTP in colorectal carcinomas. Zhang *et al*. demonstrated that PTPRT specifically regulates phosphorylation of STAT3-Tyr 705 in CRC (46). Over-expression of PTPRT activity inhibited cell growth, suggesting a tumour suppressor role (27). In addition, paxillin, a direct substrate of PTPRT, can be dephosphorylated at Tyr88 which is involved in cell-cell adhesion. Mutated PTPRT could promote CRC tumourigenesis and cell migration, while studies demonstrated the development of colon tumours in PTPRT knockout mice (48). It has been shown that *PTPRD* is frequently mutated in colon cancer (47, 49). Mutations in *PTPRD* abrogate the ability to regulate STAT3 and loss of *PTPRD* function promotes cancer progression (50).

The role of PTPRA in CRC is poorly understood. *PTPRA* mRNA levels were found to be increased 70% in late stage (Dukes' D) colorectal tumours compared to adjacent normal colon mucosa (51). Interestingly, over-expression of PTPRA increases substrate adhesion (25) and stromal invasion (52), while its silencing suppresses anchorage-independent growth and induces apoptosis in colon cancer cell lines (53).

PTPRH is also abundantly expressed in human CRC specimens (54) and CRC cell lines (29). In *PTPRH* deficient mice had normal intestinal tract, but loss of *PTPRH* inhibited tumourigenesis in mice with heterozygous mutation of the adenomatous polyposis coli gene, suggesting that *PTPRH* plays a role in promoting the intestinal tumourigenesis (55).

Another significant phosphatase that modulated JAK-STAT pathway is the low molecular weight protein tyrosine phosphatases (LMW-PTP). Malentacchi *et al*. observed an increase in the expression of *LMW-PTP* mRNA and protein level in colon tumour samples (56); clinically, overexpression of *LMW-PTP* is generally associated with a proliferative phenotype and poor prognosis (57). Here, over-expression of PRL-3 in primary colorectal tumour is associated with tumour aggressiveness (58, 59). Jiang et *al*. have shown that the loss of TGFβ signaling leads to upregulation of PRL-3 expression and activation of the PI3K/PKB pathway (60), which can promote epithelial-mesenchymal transition (61). Further on, PTEN was down-regulated by PRL-3 as shown by protein expression and IHC (62-64).

Moreover, *DUSP1* is overexpressed in colon tumours (65); Montagut *et al*. suggested DUSP1 as a potential biomarker of response to cetuximab in metastatic CRC patients (66).

Finally, Ruivenkamp and colleagues demonstrated that frequent deletion of the *PTPRJ* gene occurs in large percentage of sporadic colorectal tumours (67) and also found loss of heterozygosity at the *PRPRJ* locus in sample of human CRC (62).

4. Pancreatic Cancer

More than half of pancreatic ductal adenocarcinoma (PDAC) tissues exhibit increased PI3K and AKT expression (68-70). PH domain and Leucine rich repeat protein phosphatases (*PHLPP*) levels are markedly reduced in human PDAC that have elevated AKT phosphorylation (71). Studies have shown that PHLPP1 and PHLPP2 are able to terminate AKT signaling by directly dephosphorylating and inactivating AKT resulting in great suppression of tumour growth (72, 73).

Although *PTEN* mutations are rarely found in pancreatic cancer (74), it is important to note that *PTEN* loss of function may result in decreased sensitivity to apoptotic stimuli that could promote cellular over-growth and tumourigenesis (75-77). Chow *et al*. reported that TGFβ reduces PTEN expression and enhances pancreatic cancer cells motility through calcium-dependent PKCα (78). They also demonstrated that TGFβ down-regulates PTEN via activation of NF-κB activity (79). Mutations and changes of expression levels of TGFβ and SMAD4 proteins could be observed in pancreatic cancer tissues (80-82). SMAD4 is a tumour suppressor able to mediate signals from a family of TGFβ ligands and via phosphorylation of receptor-activated SMADs (R- SMADs) proteins forming a trimeric complex. This complex translocates into the nucleus, binds to specific DNA sequence and activates gene transcription(83). Protein phosphatase, Mg2+/Mn2+ dependent, 1A (PPM1A/PP2Cα) was identified as a phosphatase that dephosphorylates the SXS motif of R- SMADs and terminates TGF-β signaling (84).

Dual specificity protein phosphatase *6 (DUSP6*) is a cytoplasmic dual specificity phosphatase that negatively regulates members of the mitogen-activated protein (MAP) kinase superfamily (MAPK/ERK, SAPK/JNK, p38), which are associated with cellular proliferation and differentiation (85). DUSP6 dephosphorylates the active form of ERK2, which is constitutively expressed in pancreatic cancer cells (86). Moreover, *DUSP6* was reduced in invasive pancreatic carcinoma (86) and was missing in the majority of cultured pancreatic cancer cells (87, 88).

Finally, NF-κB pathway has also been implicated in pancreatic cancer (89). Based on the classical NF-κB pathway cascade, the phosphorylated IKK (IκB kinase) can further phosphorylate IκB, an inhibitory subunit of the NF-κB that is proteolytically degraded upon phosphorylation (90). Protein phosphatase 2A (PP2A) is required for signal-dependent activation of IKK (91). Inhibition of PP2A triggers apoptosis in pancreatic cancer cell line through constant activation of the NF-κB pathway (92). Li *et al*. ((93)) also suggested that treatment with cantharidin, selectively inhibits PP2A and suppresses the growth of PANC-1 cells when c-Jun N-terminal kinase pathway is over-activated.

B. Genito-urinary tumours

Renal cell and bladder cancer

Alkaline phosphatases **(**ALPL) are a group of tissue specific and tissue non-specific (TNAP) enzymes that have been previously implicated in suppressing meningiomas (94). However the relationship between ALPL levels and kidney cancer has not been established. The kidney expresses ALPL, which is used as a marker for organ function in patients' dialysis (95). High serum levels of ALPL have been associated with paraneoplastic syndrome, as observed in 77 out of 365 patients with stage II-IV renal cell carcinoma, decreasing the 5 year survival to 35.7% (96). ALPL is also used as a predictive marker for bone metastases, which is a common occurrence in patients with kidney and bladder cancer (97).

CDC25 phosphatases are frequently over-expressed in various malignancies, including RCC (98). In renal cancer cells, down-regulation of CDC25B induces a G2/M arrest and subsequent apoptosis with a concomitant reduction of the 14-3-3 protein. Furthermore, inhibition of the CDC25B reduces the rate of renal cell migration and invasion (99). Cpd5 is a selective inhibitor of CDC25 phosphatases, which acts as an anti-neoplastic agent for RCC. (100).

Serine/threonine-protein phosphatase PP1-alpha catalytic subunit (*PPP1CA*) is involved in pRb dephosphorylation and ceramide accumulation induced by RAS (101). Its role has been investigated in bladder cancer, as a potential marker for monitoring disease progression. Assessment of PPP1CA levels in urine was performed and correlated with standard cytology. Sensitivity of PPP1CA was 68.8% and the specificity was 62.7% ($p < 0.001$). A positive correlation was found between bladder cancer grade and sensitivity, while for grade 1 and grade 2 tumours, PPP1CA and other evaluated markers were even superior to cytology (102).

Protein tyrosine phosphatase, non-receptor type 21 *(PTPN21*) stimulates the Src-EGF signaling axis, and its involvement in actin cytoskeleton, cell adhesion and in regulating the stability and recycling of the EGFR has also been reported. *PTPN21* is required for growth and motility of urothelial cancer cells *in vitro*, and its high expression in human bladder cancer tissue correlates with advanced tumour stage and invasiveness. Therefore, *PTPN21* represents a novel biomarker and possible therapeutic target for bladder cancer. *PTPN21*over-expression is thought to be an early step in urothelial cancer progression. In terms of expression *in vivo*, *PTPN21* is absent from the normal bladder tissue, hyperplastic urothelium, and urothelial papilloma, whereas its expression gradually increases from low grade to high grade urothelial carcinoma (103).

In a study in clear cell RCC (ccRCC), which originates from proximal tubular tissue, microsatellite alternations at chromosome 9p23-22 (D9S168) were more common at late stage

renal cancer and associated with poor survival. The D9S168 alteration was associated with low expression of protein tyrosine phosphatase receptor delta (*PTPRD*), while IHC analysis revealed down-regulation of *PTPRD* expression in ccRCC, suggesting it as a potential tumour suppressor (104).

The *PTEN* gene is important for the growth suppression of RCC, by inhibiting cell proliferation. In renal carcinoma cell lines and primary RCC, the frequency of loss of flanking markers around *PTEN* is 20–43%, and somatic intragenic mutations are less frequent (<17%). However, the rate of PTEN inactivation at the protein level may be more frequent than that identified at the genetic level (105). A tissue microarray analysing 440 RCC specimens revealed that *PTEN* expression is typically decreased in RCC (106), and represents an early step in renal cell carcinogenesis. *A* negative correlation between pAKT and PTEN was found in primary RCC. In terms of cellular distribution, PTEN was weaker at the cytoplasmic level and stronger in the nucleus in RCC compared to normal renal parenchyma. Multivariate analyses revealed that altered expression of PTEN was associated with adverse patient outcome. (107). However, interestingly in patient samples with invasive muscular bladder cancer, PTEN was found to be located in the cell cytoplasm and a positive correlation between PTEN and pAKT was observed (108). In addition, lower PTEN expression was found in patients who died of metastases, within 5 years after surgery, compared to long-term survivors, indicating a critical role of PTEN in RCC progression. In particular, the pro-metastatic effects upon PTEN loss in RCC are achieved through Shc (109). PTEN attenuation also mediates resistance to cisplatin-induced apoptosis, through increasing levels of the cyclin kinase inhibitor p21 (110).

In primary bladder cancers loss of PTEN heterozygosity is seen in 23% of cases. Several portions of the gene were found deleted, namely that containing potential tyrosine and serine phosphorylation sites. Missense mutations in exon 1 and exon 2, that may inactivate the phosphatase activity of the PTEN gene were detected in bladder cancer cell lines derived from advanced stage bladder cancers, and were absent from a cell line derived from a lower stage cancer. However, in vivo analysis in 33 bladder cancer specimens, including the 25 T3/T4 bladder carcinomas, failed to replicate *in vitro* findings. Only 8% of the primary bladder cancer specimens are thought to harbor a mutation or homozygous deletion in *PTEN*, raising the possibility that another gene in close proximity to *PTEN* is the actual primary target of inactivation (111). In invasive bladder cancer, loss of *PTEN* in combination with altered p53 has adverse consequences and serves to identify a subgroup of patients with particularly aggressive disease, which are candidates for mTOR inhibitors as a therapeutic strategy (112). Finally, a recent mouse study found that *PTEN* deletion only influenced urothelial morphology when coupled with a deletion of LKB1 a tumour suppressor acting through TSC1 (113),.

Cyclin-dependent kinase-associated protein phosphatase (KAP) is expressed at the G1/S transition of the cell cycle and forms a complexes with cyclin-dependent kinase 2

(CDK2). KAP is over-expressed in renal cell carcinoma, while a correlation with higher histological grade has been shown (114). KAP promotes growth of RCC, and confers resistance to anti-TNFalpha induced apoptosis by preventing caspase-3 activation. Furthermore, HEK293 cells over-expressing KAP have a greater ability of cell invasion. *In vivo* xenograft models confirmed that KAP induces tumourigenicity with significantly larger xenograft tumours arising in nude mice inoculated with KAP over-expressing cells.

DUSP1 expression in renal cancer cells contributed to cell survival by attenuating the apoptosis inducing signal cascade via JNK. *DUSP1* is up-regulated at the mRNA and protein level in low-grade bladder cancers, and its expression is inversely proportional to tumour grade, suggesting its relevance in the early stages of bladder cancer development (115). *DUSP9* expression correlates with the onset of kidney carcinoma, where it is down-regulated at both the mRNA and at the protein level. Patients with tumours exhibiting low DUSP9 expression had significantly worse overall survival, with DUSP9 expression, having an independent predictive value (116).

HER-2 positive bladder cancers also exist and carry an adverse prognosis. Suppression of IFN-γ is often used as a therapeutic approach in bladder cancer patients. This treatment is probably less effective in HER-2 overexpressing/amplified tumours due to upregulated Src homology 2-containing PTPN11 signaling. A dysfunction in *PTPN11*regulation can cause abnormal cell growth and induce different kinds of cancers (117). PTPN11 is mainly expressed in the collecting duct system and in distal tubules, and hardly in glomeruli and proximal tubules. Its abundance was evident in rare renal tumours such as chromophobe RCC or oncocytoma (118).

Finally, the inhibitor of apoptosis stimulatory protein phosphatase (iASPP) is a key inhibitor of p53. iASPP is important for bladder cancer cell proliferation (119), where it has been shown that iASPP knockdown inhibits cell growth and colony formation (120).

Prostate cancer

PTEN mutations were firstly identified in multiple advanced cancers including prostate cancer (PCa), leading to its potential role as a tumour suppressor gene (121, 122). Shortly, different groups confirmed that PTEN inactivation was frequently shown in prostate cell lines, xenografts as well as primary prostate cancer (123-126). Homozygous deletion of *PTEN* in the prostate epithelium resulted in malignant prostate carcinoma displaying its association with cancer progression (127). Biological function studies showed by dephosphorylation of PIP_3 to PIP_2, PTEN tumour suppressor acts as a vital negative regulator of the PI3K/AKT/mTOR pathways affecting many aspects of cellular activity including growth and survival, whereas loss of PTEN leads to activation of these signaling cascades (77, 128). In AKT-dependent mouse model, mTOR inhibition reserved prostate intraepithelial neoplasia (PIN) through the

modulation of apoptosis and HIF-1 related pathways (129). Inhibiting PDK1, which activates AKT and S6K, prevented the development of prostate adenocarcinoma induced by *PTEN* heterozygous in mice (130). It is now clear that tumours harboring PTEN loss are highly dependent on PI3K/AKT signal for survival and proliferation. Meanwhile, inhibition of these kinases can converse the effects of PTEN loss (131). Therefore, pharmacological targeting PI3K/AKT and mTOR kinases have provided potential therapeutic importance in PTEN null cancers, including PCa. Indeed, several molecules including PI3K inhibitor (XL147), AKT inhibitor (perifosine) and mTOR inhibitors (CCI-779 and RAD001) are under clinical development (132).

Furthermore, PTEN loss was shown to play an important role in the survival crosstalk between PI3K/AKT and androgen receptor (AR) in PCa progression. Upon acute androgen ablation in human PCa cell line LNCaP, PTEN inactivation displayed increased activity of the PI3K/AKT axis indicating a possible compensating phenomenon across PI3K/AKT and AR signaling (133, 134). Prostate cancers with *PTEN* null relapsed after androgen withdrawal and enjoyed the capability of growth in the absence of androgen. Moreover, global analysis of genomic alterations elicited by homozygous *PTEN* deletion identified genes associated with cancer metastasis (135). In addition, it has been reported that PTEN can suppress the transcriptional activity of AR and cell proliferation induced by androgen as well as prostate-specific antigen, whereas androgens prevented PCa cells from PTEN-dependent apoptosis in the presence of AR (136). Similar evidence described that PTEN can directly interact with AR resulting in an inhibition of the AR nuclear translocation and an increase of the AR degradation in a PI3K/AKT independent manner, while in PTEN-null context both AR expression and activity were elevated compared with wild-type MEFs (137). Collectively, PTEN loss may lead to a gain-of-function of AR in both PI3K/AKT dependent and independent environment. Coordinately, loss of PTEN and intensified AR may contribute to tumourigenesis and androgen refractory PCa.

Pro-apoptotic protein Par-4 was shown to be essential for PTEN-dependent apoptosis, while AKT can directly bind to Par-4 and inhibit its activity through phosphorylation resulting in the survival of prostate cancer cells (138). Recent studies demonstrated that Par-4 inactivation associates with PTEN loss in a high percentage of human prostate carcinomas. Similar to PTEN-heterozygous mice, Par-4-null mice only developed benign prostate lesions, whereas simultaneous Par-4 loss and PTEN haploinsufficiency caused invasive prostate cancer in mice through activating AKT signaling as well as NF-kappaB pathway (139).

PP1 and PP2A are two major classes of serine/threonine protein phosphatases involved in many different cellular processes, including survival, cell cycle and apoptosis through dephosphorylation of key regulators such as PKA, AKT, PKC and glycogen synthase kinase 3 (GSK3) (140, 141). PP2A comprises of several subunits: scaffolding, catalytic and regulatory. Each subunits of PP2A exists in at least two isoforms (142, 143). *PPP2CA* levels

were found decrease in majority of androgen-independent PCa cell lines and in cancer lesions as compared with the adjacent normal/benign tumour tissues (144). *PPP2R2A*, a potential tumour suppressor gene, was found commonly deleted among PCa with homozygous deletions and no significant association between common single nucleotide polymorphisms of *PPP2R2A* and sporadic prostate cancer. These findings suggested that it may play an important role in prostate cancer tumourigenesis on somatic levels (145). In PCa, caveolin-1 was shown to bind to and inhibit PP1 and PP2A resulting in AKT activity enhancement indicating an important interplay involving both two phosphatases in tumourigenesis (146). Recent studies showed that PP1 can regulate AR protein stability and cellular localization via dephosphorylation of Ser-650 (147). 2,4,3',5' tetramethoxystilbene (TMS), a synthetic trans-stilbene analog, was able to induce PP2A activation leading to inhibition of AKT. This in turn stimulated expression of cell cycle inhibitor p27(kip1) in PC-3 cells (148). A failed recruitment of PP2A-Bα by TGF-β type I receptor was suggested to be partly responsible for TGF-β abundance in malignant prostate cells (149). Moreover, PP2A activity was decreased in androgen-independent PCa cells (C4-2) compared with androgen-dependent LNCaP cells, whereas inhibition of PP2A enabled LNCaP cells to grow in an androgen-deprived condition (150). Sodium selenate, a specific selenium-containing compound, was identified as PP2A activator which significantly augmented the activity of PP2A, thereby inhibiting VEGF-induced growth and vessel branching of endothelial cells, and obstructing tumour neovascularisation. This anti-angiogenisis effect via PP2A allowed it into a phase I study in patients with castration-resistant PCa and results showed a similar effect to other anti-angiogenic agents (151, 152).

The cell division cycle 25 (CDC25) families are dual specificity phosphatases functioning in activation of cyclin-dependent kinases (CDK), which in turn modulate cell cycle progression. In mammalian cells, three isoforms have been identified: CDC25A, CDC25B and CDC25C (153). CDC25A and CDC25B were shown to be overexpressed in human PCa tissues and high Cdc25B associated with high Gleason scores and aggressiveness in PCa (154, 155). These two different studies also demonstrated that CDC25A can suppress androgen-responsive promoter via physically interaction with AR, whereas CDC25B can function as a coactivator or AR in a hormone-dependent manner in LNCaP. Similarly, CDC25C expression was elevated in PCa in comparison with normal prostate tissues and its spliced isoform was also found to be correlated with increased growth in PCa (156). Theaflavin (TF), a black tea polyphenol, can cause G2/M phase arrest in PC-cells by inducing cyclin kinase inhibitor p21 (waf1/cip1) and inhibiting CDC25C and cyclin B (157). Taken together, several studies have shown that CDC25 family phosphatases are important players in PCa progression and may provide potential therapeutic targets in PCa.

SHP1, an SH2 domain-containing protein tyrosine phosphatase, was detected in normal prostate, benign prostate hyperplasia, prostate epithelial cells and well differentiated adenocarcinoma, whereas diminished SHP1 expression was observed in malignant prostate

tissue and poorly differentiated advanced prostate cancer (158-161). Moreover, SHP1 overexpression decreased PC-3 cell proliferation (159). Tassidis *et al*. demonstrated the expression of SHP1 mRNA and protein in two human prostate cancer cell lines, LNCaP and PC-3, were at different levels (161). In this study, silencing SHP1 in LNCap, which expresses high amount of endogenous SHP1 protein, exhibited an increase in cellular proliferation and cyclin D1. In contrast, in PC-3 cells, with low endogenous level of SHP-1 expression, overexpression of SHP-1 resulted in a decrease in proliferation and cyclin D1. A recent study showed that depletion of SHP1 in PC-3 cells caused G1 phase cell-cycle arrest by increasing p27 protein stability, due to its capability of regulating PI3K/AKT pathway and cyclin-dependent kinase 2 (CDK2) activity. This indicated that SHP1 may play a role in the regulation of cell cycle progression (162).

SHP2, an SH2 domain-containing protein tyrosine phosphatase sharing homology with SHP-1, is also expressed in prostate cancer cell lines including PC-3, DU145, LNCaP and LNCap-IL6+ as well as patient specimens with PCa. SHP2 staining from 122 patients showed that low cytoplasm intensity associated inversely with prostate volume while staining in the nuclear was positively correlated with extracapsular extension. This implicated that SHP-2 ablation in the cytoplasm correlated with enhanced tumour growth (163). However, other studies reported that SHP2 may act as a proto-oncogene product by increasing Ras-MAPK signaling (164).

C. Gynaecologic tumours

1. Endometrial cancer

There are two main types of endometrial cancer (EC) namely type-I, which is estrogen receptor and progesterone receptor positive with low grade and type-II with clear-cell or serous morphology and high grade (165), (166, 167). Currently, endocrine and chemotherapy are being used to treat type-I EC (168). Although most clinical trials and treatment regimens do not stratify patients according to type, research at molecular level have identified distinct genetic alterations and signaling pathways between the two types. For example, type I cancer frequently has deregulated PI3K/PTEN/AKT pathway and loss of PTEN function while type-II has alterations in P53 and /or P16 pathways along with over expression and amplification of HER2.

PP2A is a well-known tumour suppressor which inhibits RAF-MEK-ERK pathway by inhibiting activity of ERK and RAF besides inhibiting the downstream signaling of RAS pathway via de-phosphorylation and inhibition of c-Myc, RALA and AKT. Depending on the type of cancer, this function of PP2A has been shown to be mediated by regulatory β subunits (169). On the contrary, somatic missense mutations in PPP2R1A, which encodes the α-isoform of the PP2A scaffolding subunit, were demonstrated in high-grade serous endometrial tumours (170).

Constitutive activation of MAPK pathway is known to play an important role in EC and since DUSP6 can negatively regulate ERK2, Chiappinelli *et al.* studied its methylation status in EC. They identified that silencing of DUSP6 is uncommon and unlikely to cause activation of MAPK pathway in EC (171). On the other hand, LMW-PTP, was studied and a significant association was identified in low grade EC with genotypes carrying the *C allele along with high concentration of S isoform (172).

Finally, Jay *et al.* studied the role of phosphatases in determining racial inequality in EC. Using microarray they identified phosphoserine phosphatase (*PSPH*), which is essential for the synthesis of L-serine, and designated phosphor-serine phosphatase like *(*PSPHL*)* as the most over-expressed genes in EC in African-Americans when compared to Caucasians (173).

2. Cervical cancer

The role of Protein phosphatase 1 (PP1) in tumour metastasis was studied by knockdown of PP1 and its regulator NIPP1 in HeLa cells. Knockdown of PP1 prevented migration of HeLa cells by inhibiting Cdc42 signaling pathway (174).Zeng *et al.* identified Protein phosphatase 1 inhibitor 5 (IPP5) as a tumour suppressor in cervical cancer; over-expression of mutant IPP5 in HeLa cells, caused G2/M arrest both *in vitro* and *in vivo* via inhibition of ERK activation (175). Furthermore, Protein phosphatase 1, regulatory subunit 7 (PPP1R7) was shown to be significantly up-regulated in metastatic CC patient samples after radiotherapy (176). Moreover, hSHIP, a human SH2-containing inositol-5-phosphatase, has also been shown to inhibit growth and act as a tumour suppressor in CC. *In vitro* and *in vivo* studies by He *et al.* have shown that stable over expression of hSHIP induces S-Phase arrest along with down regulation of AKT1/2 expression and phosphorylation, thereby inhibiting proliferation of cervical cancer HeLa cells (177). Taken together, PP1 and its regulatory subunits along with hSHIP, play an important role in progression and therapeutic response in CC and can prove to be new therapeutic targets.

Dual specificity phosphatase 3 (*DUSP3*) is known to dephosphorylate ERK1/2 and JNK1/2 MAPK kinases, which are key regulators of cellular differentiation, proliferation and apoptosis. In CC, knockdown of DUSP3 inhibited the growth of HeLa cervical cancer cells by increasing the expression of cyclin dependent kinase inhibitor, p21 and inhibiting G1-S and G2-M cell cycle transition (178). This *in vitro* study was further supported by detection of increased expression and nuclear localization of DUSP3 in cervix cancer cell lines when compared to normal keratinocytes as well as in HPV positive cell lines when compared to HPV negative cell lines. Furthermore, increased expression was identified in primary cervix cancer biopsies, including squamous cell carcinomas of unterine cervix and squamous intra epithelial lesions indicating potential use of DUSP3 as a new marker for progression of CC and as a new target for anticancer therapy (179). Small-molecule inhibitors for DUSP3 have been developed

which can inhibit enzymatic activity of DUSP3 at nanomolar concentrations while inhibiting the proliferation of cervix cancer cell lines without affecting proliferation of primary normal keratinocytes (180).

PP2B or serine/threonine phosphatase calcineurin (CaN) was shown to promote CC cell proliferation by directly interacting and enhancing c-Jun protein stability and activity. This was confirmed in cervical tissue samples that showed decreased phosphorylation of c-Jun and enhanced PP2B and c-Jun expression (181). In contrast,PP2B was shown to be down-regulated in malignant squamous carcinomas (182). This inconsistency might be due to the small number of samples used in both the studies and requires further investigation. On the other hand, no mutations were identified in *PPP2R1B gene* which encodes the beta isoforms of the subunit A of the PP2A between normal and cancer (183).

Expression of SHP-2 tyrosine phosphatase, was negatively associated with IFN-β expression in CC while its silencing inhibited growth of SiHa CC cell line by inducing expression of IFN-β, (184). Other phosphatases that can either inhibit or promote CC include hSHIP, a human SH2-containing inositol-5-phosphatase and DUSP-3 respectively (177, 179, 180).

Cancerous inhibitor of protein phosphatase 2A (CIP2A) was shown to be over expressed in CC when compared to normal tissue by IHC and RT-PCR. More importantly, papillomavirus 16 E7 oncoprotein directly upregulated CIP2A expression which could enhance proliferation and growth of CC cells by modulating c-Myc expression (185).

Finally, mutation and loss of PTEN has also been shown to drive tumourigenesis here (186, 187), as previously described.

3. Ovarian cancer

Inactivation of PTEN, by genetic mutation is well-known in ovarian cancer (OC) (188). Several *in vitro* studies have shown that PTEN can regulate growth, invasion, migration and resistance to chemotherapy in OC (189-193). Interestingly, PP2A has been shown to regulate PTEN; inhibition of PP2A decreased the expression of PTEN and enhanced phosphorylation of PTEN and AKT, causing increased migration/invasion of OC in fibrillar collagen, indicating PP2A as a tumour suppressor in OC. This was further supported by detection of decreased expression and activity of PP2A in OC tissue (194).

Expression of CIP2A, studied in 562 serous ovarian cancer patients by IHC, showed strong cytoplasmic staining in 40% of the samples and was associated with high grade, advanced stage and poor outcome (195).On the other hand, inhibition of PP2A was essential for the apoptosis induced by doxorubicin (196) and translocation of PP2A to plasma membrane was essential for gonadotropin-releasing hormone (GnRH) antagonist, cetrorelix induced apoptosis in GnRH responsive ovarian cancer cells (197).

A study by Manzano *et al.* evaluating the expression of 68 phosphatases in ovarian epithelial and cancer cell lines identified a 10-25 fold higher expression of DUSP1 in normal compared to malignant OC cell lines. This was confirmed by IHC staining in normal and OC specimens and was shown to be a critical factor in the progression of cancer (198).

PTPN13as found to be increased both at RNA and protein level in Fas resistant OC cell lines as well as in OC patient samples studied using tissue microarray (199). Knockdown of PTPN13 using siRNA enhanced the sensitivity of SKOV3 cells to carboplatin indicating that it can play a key role in carboplatin resistance (200).

In 106 OC patient samples, cell cycle related phosphatases, CDC25A and CDC25B were found to be commonly expressed and were associated with poor prognosis independent of tumour grade, histotype, stage and residual tumour after surgery, thereby, indicating potential role of these phosphatases to be used as prognostic factors (201).

Using northern blots and immunoblotting , Mok *et al.* have shown that PTPN6 was over expressed in 7 of the 8 ovarian epithelial carcinoma cell lines both at RNA and protein level along with over-expression in invasive ovarian epithelial cancer tissues (202).

Cisplatin is one of the most widely used drugs for treating OC. Sensitivity to Cisplatin is known to be partly mediated by activation of p53 by checkpoint kinase 1 (CHK1). Protein phosphatase magnesium-dependent 1 (PPMD1) is known to deactivate p53 and Chk1 via dephosphorylation. Using cisplatin resistant cell lines, Ali *et al.* showed knockdown of PPMD1 can re-sensitize resistant cells to cisplatin by activating P53 and CHK1 (203). Moreover, PPM1D was shown to be highly expressed at mRNA level in ovarian clear cell carcinoma cell lines with amplification at 17q23.2 and was amplified in 10% of primary clear cell carcinomas (204). The role of protein phosphatases in cisplatin sensitivity was also studied by Bansal *et al.* and they identified that patients with incomplete response to cisplatin had two-fold lower PP2C levels when compared to those with complete response. This was confirmed by western blotting in platinum-resistant OC cells (205). Moreover, genome-wide expression profiling of SK-OV-3 ovarian cancer cells identified two regulatory subunits of PP2A as key mediators of sensitivity to cisplatin and knockdown of each subunit by RNA interference made OC cells more responsive to cisplatin (206).

Polato *et al.* studied the role of PRL-3 in OC and expression of PRL-3 mRNA was found to be higher in stage III OC samples when compared to stage I samples and by using siRNA, PRL-3 was shown to be important for growth of OC cells *in vitro* (207, 208). Moreover, PRL-3 regulated migration and invasion of OC cells by interacting with integrin α1, inhibiting phosphorylation of integrin β1 and enhancing the downstream phosphorylation of Erk1/2(209). *In vivo* mice studies have shown that monoclonal antibodies against PRL-3 can prevent both tumour growth and metastasis of ovarian cancer cells making it a potential target for therapy in OC (210).

Finally, Tanyi *et al.* identified decreased mRNA expression of phosphatidic acid phosphatase type 2A (PPAP2A, LPP-1) in OC, which is known to degrade lysophosphatidic acid that can promote tumour growth and metastasis (211).

D. Other tumours

Lung cancer

Several phosphatase (PTPases) have been identified to play a role in this malignancy. Omerovic J. *et al*. performed a phosphatome RNAi screen in A549 lung cancer cells and ranked their effects on phosphorylation of AKT-Ser473. Although, phosphatase and tensin homolog *(PTEN)* appeared to be the main factor involved in inhibiting the oncogenic *K-Ras*, other phosphatases have been identified with similar potencies including protein tyrosine phosphatase non-receptor type 2 (*PTPN2*) and protein tyrosine phosphatase non-receptor type J (*PTPRJ*) (212). PTEN protein expression was reduced or lost in 74% of lung tumours, with loss occurring more often in well to moderately differentiated tumours. In NSCLC, loss of PTEN protein expression occurs frequently, although the mechanism responsible for loss is not clearly attributable to deletion or epigenetic silencing. *PTEN* loss may also be a favorable prognostic marker, although further studies are needed to confirm this finding (213). Scrima *et al*., have suggested protein tyrosine phosphatase non-receptor type 13 (*PTPN13*) as candidate tumour suppressor gene in NSCLC. This gene is frequently inactivated in NSCLC through somatic mutation (approximately 8%) or due to loss of protein expression (approximately 73%); *PTPN13* negatively regulates anchorage-dependent and anchorage-independent growth of NSCLC cell lines *in vitro* (214).

The CDC25 phosphatases are known to play an important role in cancer cell growth. Increased expression of cell division cycle 25 homolog B (*CDC25B*) has been reported in tumours of different tissue origins, including NSCLC. Analysis of primary tumours and corresponding healthy lung tissues from 177 patients with NSCLC revealed an over-expression of *CDC25B* in 45.76% of the samples. Moreover, high expression of *CDC25B* correlated with positive expression of endothelin-, and with the number of intratumoural microvessels. Statistical analysis of survival data revealed that elevated *CDC25B* expression was significantly associated with shorter disease-free and overall survival, suggesting that *CDC25B* might play an important role in the angiogenic process and in determining the prognosis of patients with NSCLC (215).

Another protein known to play a role here is the dual specificity phosphatase 1 (DUSP1). It has been shown that down-regulation of *DUSP1* induced changes in the expression levels of genes involved in specific biological pathways, including angiogenesis,

MAP kinase phosphatase activity, cell–cell signaling, growth factor and tyrosine-kinase receptor activity. Changes in the expression of some of these genes were due to modulation of c-Jun-N-terminal kinase and/or p38 activity by *DUSP1*. Another report showed that silencing of *DUSP1* inhibits invasion and metastasis in NSCLC tumour (216).

Moreover, Chitale *et al*. examined 199 lung adenocarcinomas by integrating genome-wide data on copy number alterations and gene expression and revealed that non-random patterns of copy number alterations are linked to *EGFR* and *KRAS* mutation status. They also discovered a striking association of *EGFR* mutations with under-expression of dual specificity phosphatase 4 (*DUSP4*), which is involved in negative feedback control of *EGFR* signaling. Clinically, *DUSP4* loss has a significant impact on overall survival, further supporting its biological significance in lung adenocarcinomas.

DUSP4 loss also associates with *p16/CDKN2A* deletion and defines a distinct clinical subset of lung cancer patients (217).

Another phosphatase that seems to play a role in tumourigenesis is the protein tyrosine phosphatase non-receptor type 12 (*PTPN12*), by regulating cell adhesion and migration. However, the mechanism by which *PTPN12* is regulated in response to oncogenic signaling is unclear. Zheng *et al*., have shown that *Ras* induces extracellular signal-regulated kinase 1 and 2 (ERK1/2)-dependent phosphorylation of PTPN12 at Ser-571, which recruits peptidylprolyl cis/trans isomerase, NIMA-interacting 1 (PIN1) to bind to PTPN12. Isomerization of the phosphorylated PTPN12 by PIN1 increases the interaction between PTPN12 and focal adhesion kinase (FAK, PTK2) which leads to dephosphorylation of FAK-Tyr397 and the promotion of migration, invasion, and metastasis of v-H-Ras-transformed cells (218).

Breast Cancer

Up-regulation of PTPN1 was first described in human BC cell lines over-expressing the *neu* oncogene (219). Wiener *et al.* reported a correlation between increased expression of PTPN1 and HER2 expression human mammary tumours compared with normal breast tissue (220). Global deletion of PTPN1 either delayed or protected against mammary cancer in mice, depending on the HER2/Neu allele and mice strain used (221, 222), suggesting that inhibition of PTPN1 may be a potential target for treating breast cancer. Targeted PTPN1 silencing in the mammary epithelium of either established mouse tumours, or in human BC cells xenografts grown on HER2 positive mice has been shown to delay the early onset of formation of mammary tumours (223).

Recent studies indicate that PTPN13 may be effective therapeutic target for the treatment of breast cancer. Lower levels of PTPN13 have been described in BC and metastatic tissue specimens (224) and increased expression of PTPN13 is associated with a favorable outcome in BC patients (225). Over-expression of PTPN13 is sufficient to block the

IRS-1/PI3K/MAPK pathway (226). In addition, over-expression of PTPN13 in combination with anti-estrogen treatment increased apoptotic cell death by the reduction of IGF-1 induced IRS-1 and AKT phosphorylation (227). PTPN13 can also inhibit tumour aggressiveness via the direct dephopshporylation of Src at Y419 (224), which is upregulated in tamoxifen resistance ER-positive breast cancer patients (228). New therapeutic routes using tamoxifen and SRC inhibitors are currently being examined (229, 230).

Loss of functional PTEN has been described in primary and metastatic breast tumours (231, 232) resulting in hyperactivation of the PI3K pathway and an increase in cell proliferation (233). Down-regulation of PTEN activity and activation of the PI3K signaling pathway is associated with resistance to anti-estrogen therapy (234). Screening for PTEN mutations may identify BC patients who may benefit from treatment with AKT inhibitors. In this regard, BC cell lines with PTEN mutations were recently described to have increased sensitivity to the novel AKT inhibitor MK-2206 (235).

Several other PTP's have a tumour suppressor function in BC. PTPN12, has been shown to act as a potent tumour suppressor in triple negative breast cancer cells and is more frequently inactivated in this BC subtype. Genetically silencing *PTPN12* induces transformation and disrupts acinar formation in mammary epithelial cells (236). Levels of cytoplasmic protein tyrosine phosphatase non-receptor type 9 (PTPN9) inversely correlate with STAT3 in BC tissue (237). PTPN9 has been reported to inactivate STAT3 following EGFR dephosphorylation in breast cancer cells (238), suggesting that PTPN9 may play a critical role in BC development.

A number of DUSPs are dysregulated in BC. The majority of breast carcinomas, including both poorly differentiated and metastatic stages disease, express higher levels of DUSP1 compared to normal breast tissue (65, 239). Studies suggest that inhibition of DUSP1 may be an effective therapeutic target against chemoresistance in BC patients. Increased expression of DUSP1 has been shown to correlate with decreased JNK activity (239). Overexpression of DUSP1 in BC cell lines treated with chemotherapeutic agents, which target the JNK pathway, protects against apoptosis. Conversely, genetic or chemical silencing of DUSP1 enhances sensitivity to chemotherapeutics agents (240), indicating that combination therapies that target this enzyme may be effective in the treatment of BC.

DUSP3, DUSP4 and DUSP5 also negatively regulate ERK signaling. DUSP4 up-regulation has been described in BC tumours (239). Deficiency of DUSP4has been identified as a mechanism of neoadjuvant drug chemoresistance in breast cancer tumours. DUSP4 depletion is frequently found in chemotherapy refractory tumours which are associated with increased cell proliferation and basal-like BC status. Over-expression of DUSP4either in breast cancer cell lines or in BC xenograft mouse models increased chemotherapy-induced apoptosis, whereas depletion reduced chemosensitivity (241). Upregulation of DUSP3 and DUSP5 has been reported in PMA-treated MCF-7 and BKBR3 breast cancer cell lines. Activation of the

ERK1/2 pathway and accelerated growth arrest of BC cells, has been observed following silencing of either DUSP3 or DUSP5, and overexpression of either phosphatase prevents growth inhibition and cell migration (242).

The novel phosphatase, VHZ (VH1-like (member Z)), encoded by the DUSP23 gene, is also associated with BC and has been identified in some invasive ductal and epithelia BC tumours. VHZ has been shown to localise to the centrosome and enhance G1/S cell cycle progession, suggesting that this enzyme may be a potential chemotherapeutic target (243).

All three CDC25 isoforms (CDC25A, CDC25B, CDC25C) can regulate G_1/S and G_2/M cell cycle transition (153). CDC25A overexpression is associated with poor survival in BC patients (244-246). In addition, CDC25A 263C/T and -51C/G polymorphisms gene polymorphisms are associated with BC incidence and metastatic potential have been identified in BC patients, suggesting that CDC25A gene may be candidate markers for earlier diagnosis and targets for BC therapy (247). Recent studies have demonstrated increased Fox1 activity following CDC25A-indcued dephosphorylation of CDK2. Inhibition of CDC25A inhibits metastases in BC mouse models, suggesting that this phosphatase may be a potential target for advanced stages of the disease (248).CDC25B is overexpressed in primary BC tumours (249), although expression levels do not always correlate with an aggressive phenotype (250). CDC25C splice variants have been found to shift or be elevated in BC cell lines, particularly in cell lines with multi-drug resistance or those treated with sub-lethal levels of genotoxic agents (251, 252), suggesting that CDC25C splicing may be an additional regulatory event involved in cellular response to DNA damage in BC cells.

The oncogene SRC3, which is overexpressed or amplified in the majority of breast cancer tumours (253), is a target for PP1. PP1 can block proteasome-dependent turnover of SRC-3 by dephosphorylation at Ser-101 and Ser-103, resulting in the stabilisation of SRC-3 (254). Increased expression of mutated PP2A at the active phosphatase site pY307 has been reported in HER2/neu BC tumours, which significantly correlated with disease progression (255). Loss of PP2A activity in HER2/neu positive BC cells resulted in apoptotic cell death mediated by p38 MAPK caspase-3 PARP activation (256), suggesting that this phosphatase may be a potential therapeutic target in BC.

MCF7 cells carry an amplified PPM1D/Wip-1 gene and overexpress PPM1D phosphatase protein. Silencing PPM1D has been reported to enhance doxorubicin-induced apoptosis due to p53-mediated phosphorylation of Bax (257).

Over-expression of the Eyes Absent (EYA) family of proteins, which are essential co-activators of the Six1 family of homeobox transcription factors, have recently been reported to enhance the proliferartion, migration and invasiveness of BC cells (258). Silencing of EYA2 in MCF7 cells reverses the ability of Six1 to induce TGF-B signaling and induce characteristics associated with epithelial-mesenchymal transition (259). High-throughput screening assays have recently identified a series of specific small molecule EYA2 phosphatase inhibitors that

may be useful for the development of future BC therapies (260).

Sarcomas

Sarcomas are probably even more heterogenous than all the aforementioned tumour types (261).

PP2A has been identified in a protein array screen for interacting proteins with the Kaposi's sarcoma-associated herpesvirus (KHSV) LANA protein, which functions in latently infected cells as an essential component of KSHV replication and dysregulated cell growth. The subunits PP2A and PP2B, but not the catalytic subunit PP2C, were found to associate with LANA, suggesting that PP2A activity may be dysregulated in this sarcoma (262).

Alterations in PTEN expression have been described in several types of sarcoma. PTEN up-regulation has been described in 80% of tissue samples from Kaposi's Sarcoma biopsies, with 58% having expressing phosphorylated PTEN (263). PTEN losses and mutations are also a frequent occurrence in the malignant smooth muscle neoplasm, leiomyosarcoma (264-266).

SHP2 may be a promising therapeutic target for Kaposi's sarcoma. Constitutive activation of the vGPC receptor, the Kaposi's herpes sarcoma virus associated chemokine has been shown to result in the phosphorylation of SHP2 (267). The vGPCR contains a bona fide immunoreceptor tyrosine-based inhibitory motif (ITIM) that binds and constitutively activates Shp2 (268). Moreover, SHP2 is required for vGPCR activation of the MEK-ERK1/2 axis, the transcription factors AP-1 and NFκB and vGPCR-induced endothelial cell migration (267).

PTPN13 is highly expressed in Ewing's Sarcoma family tumours (ESFT) cell lines and in patient tumours, with higher expression levels in metastatic compared to primary tumours. PTPN13 has been found to associate with the abberant transcription factor EWS-11, and is up-regulated following overexpression of EWS-11(269). MK-STYX, which encodes for a MAP-kinase phosphatase-like protein, is also constitutively expressed in EFST and may be a putative target for therapy in this class of tumours (270).

Conclusions

Phosphatases, like kinases, represent molecular switches that can turn on or off a variety of signaling pathways (**Fig 1**) resulting in abnormal cellular processes including uncontrolled proliferation, differentiation, angiogenesis and metastasis. Thus far, a large number of phosphatases has been associated with the development and progression of different types of cancer (**Table 1**). Further understanding and clarifying the involvement and role of phosphatases in signal transduction would be very helpful in developing new effective drugs to be used alone or in combination with other therapeutics for cancer treatment.

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Conflict of interest

The authors declare no conflict of interest.

Table Alterations observed in phosphatases and resulting malignancies.

Gene symbol	Uniport KB	Expression
PTEN	P60484	lung(213), esophageal(1-3), pancreatic(74), kidney(106), bladder(111), cervical(186, 187), ovarian(188), breast(231, 232), sarcoma(263), prostate(123-126)
PTPN1	P18031	gastric(15, 271), colorectal(42), breast(219)
PTPN2	P17706	lung(212)
PTPN3	P26045	gastric(18), colorectal(27)
PTPN4	P29074	gastric(18, 22)
PTPN6	P29350	gastric(13), ovarian(202), prostate(158-161)
PTPN9	P43378	breast(237)
PTPN10	P28562	lung(216), gastric(30), colorectal(66, 272), bladder(115), ovarian(198), breast(239, 272)
PTPN11	Q06124	gastric(9, 10), kidney(118), cervical(184), sarcoma(267), prostate(163)
PTPN12	Q05209	lung(218), esophageal(6), breast(236)
PTPN13	Q12923	lung(214), colorectal(27, 41), ovarian(199), breast(225), sarcoma(269)
PTPN14	Q15678	colorectal(27)
PTPN21	Q16825	bladder(103)
PTPN23	Q9H3S7	colorectal(27)
CDC25A	P30304	esophageal(4), ovarian(201), breast(244-246), prostate(155)
CDC25B	P30305	lung(215), esophageal(4), kidney(99), ovarian(201), breast(249), prostate(154)
CDC25C	P30307	breast(251, 252), prostate(156)
DUSP3	P51452	cervical(179), breast(242)
DUSP4	Q13115	lung(217), breast(239, 241)
DUSP5	Q16690	breast(242)
DUSP6	Q16828	pancreatic(86-88), endometrial(171)
DUSP23	Q9BVJ7	breast(243)
PTPRA	P18433	gastric(22, 26), colorectal(51, 53)
PTPRB	P23467	gastric(22)
PTPRD	P23468	colorectal(47, 49), kidney(104)
PTPRF	P10586	colorectal(27)
PTPRH	Q9HD43	gastric(22, 29), colorectal(29, 54, 55)
PTPRJ	Q12913	lung(212), gastric(22), colorectal(62, 67)
PTPRG		colorectal(27)
PTPRN	Q16849	gastric(22)
PTPRO	Q16827	esophageal(7), colorectal(27)
PTPRT	O14522	gastric(28), colorectal(27, 46, 48)
PTPRZ	P23471	gastric(22)
PTP4A3	O75365	gastric(31-36), colorectal(58, 59), ovarian(207, 208)
LMW-PTP	P24666	colorectal(56)
PHLPP1	O60346	pancreatic(71)
PPP1CA	P62136	bladder(102), cervical(174), prostate(146, 147)
PPP1CB	P62140	
PPP1CC	P36873	
PPP2CA	P67775	pancreatic(92, 93), cervical(182), endometrial(170), ovarian(194), breast(255), sarcoma(262), prostate(144-146)
PPP2R2A	P63151	
PPP2R1B	P30154	
PPM1D	O15297	ovarian(204), breast(257)
ALPL	P05186	kidney(97), bladder(97)
CDKN3	Q16667	kidney(114)
PSPH	P78330	endometrial(173)
PPAP2A	O14494	ovarian(211)
EYA2	O00167	breast(258)

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