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Prostate Cancer Dephosphorylation Atlas

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1. Introduction

The widespread nature of protein phosphorylation/dephosphorylation underscores its key role in cell metabolism. Phosphate moiety balance on proteins is regulated by protein kinases (PK) and protein phosphatases (PP), which are milestone players of eukaryotic signaling pathways. In general, signaling proteins involved in intracellular pathways are transiently active or inactive by phosphorylation and dephosphorylation mechanisms, covalently executed by PK and PP, respectively (Hooft et al. 2002; Tonks, 2005). It is accepted that the phosphorylation state of these proteins must be kept at a dynamic equilibrium in biological systems. Any deviation in this balance (generally associated with augmented PK signaling) can cause the intracellular accumulation of serine, threonine, tyrosine-phosphorylated proteins, which will cause abnormal cell proliferation and differentiation, thereby resulting in different kinds of diseases (Souza et al., 2009). Similar deviation from this equilibrium can be also induced by decreased activity of protein tyrosine phosphatases (PTP) resulting from gene mutation or gene deletion, leading to an increase in tyrosine phosphorylated proteins in cells. PPs are subdivided into two major families, with regard to their physiological substrates: protein tyrosine phosphatases and serine/threonine phosphatases. In particular, tyrosine phosphorylation of key proteins is a critical event in the regulation of intracellular signaling pathways (Aoyama et al., 2003; Gee and Mansuy, 2004; Souza et al., 2009). There is strong evidence pointing that low SHP-1 PTP activity is associated with a high proliferation rate and an increased risk of recurrence after radical prostatectomy for localized prostate cancer (Tassidis et al., 2010). Moreover, it has been proposed that specific PTPs may be related to determining the developmental stage and aggressiveness degree of prostate cancer (Chuang et al, 2010). Thus, it is reasonable to suggest that the chemical modulation of PTPs may, therefore, be a good spot for pharmacological intervention for overcoming prostate cancer, in combination with conventional cancer chemotherapeutic strategies. However, the critical bottleneck in deciphering the role of PTPs in prostate cancer biology is the identification of their physiological substrates and how their enzymatic activity is related to molecular changes in proliferation and cell death. In this chapter we shall focus on the contribution of the low molecular weight protein tyrosine phosphatase (LMWPTP), Src homology 2 (SH2) domain-containing PTP (SHP-1), cell division cycle 25 (Cdc25), acid phosphatase, phosphatase and tensin homolog (PTEN) and dual-specificity phosphatase (DUSP) for prostate carcinogenesis and describe their participation in the molecular events that lead to tumor survival and

osteomimetic properties, highlighting perspectives and directions for future research that improve current knowledge on these critical signaling molecules.

2. Protein phosphatases

The ubiquitous nature of protein phosphorylation/dephosphorylation underscores its key role in cell signaling metabolism, growth and differentiation. In fact, cells respond to internal and external stimuli through integrated networks of intracellular signaling pathways that act via cascades of sequential phosphorylation or dephosphorylation reactions which are governed by the action of PK and PPs, respectively (Hooft van Huijsduijnen et al., 2002; Tonks, 2005).
PPs have been classified by structure and substrate specificity into protein serine/threonine phosphatases (PSTPs) and protein tyrosine phosphatases (PTPs) (Aoyama et al., 2003; Gee and Mansuy, 2005).
In general, PTPs control fundamental physiological processes such as cell growth and differentiation, cell cycle, metabolism, immune response and cytoskeletal function. Furthermore, interfering with the delicate balance between counteracting PTKs and PTPs is involved in the development of numerous inherited and acquired human diseases such as autoimmunity, diabetes and cancer (Alonso et al., 2004; Andersen et al., 2004; Ferreira et al., 2006; Souza et al., 2009; Zambuzzi et al., 2010; Zambuzzi et al., 2011).

2.1 PTPs classification

Up to now, 107 genes encoding PTPs have been discovered in the human genome, whereas 81 of them have been predicted to be active PTPs (Alonso et al., 2004). Classically, PTPs were divided into four classes: receptor type PTPs, non-receptor PTPs, dual specificity PTPs and low molecular weight PTPs. However, some authors have proposed an alternative way to classify this enzyme family based on the amino acid residues of their catalytic domains (Alonso et al., 2004; Bialy and Waldmann et al., 2005). In fact, comparison of the crystal structure of the PTPs that have been solved to date demonstrates that the PTPs domains are conserved in both sequence and structure. Additionally the sequences (domains) outside the catalytic domain are diverse and may regulate PTP activity and/or function (Table 1).

- Class I cysteine-based PTPs catalyze the enzymatic reaction in which an active-site cysteine group plays a central role and renders the PTP susceptible to oxidant agents that can lead to oxidation of the key cysteine and inhibition of PTP activity. This class contains the "classical" PTPs and the "dual specificity" protein phosphatases (DSPs), both evolved from a common ancestor. The "classical PTPs" members are strictly tyrosine-specific and according to their subcellular localization can be further divided into intracellular PTPs (PTP1B and SHP) and receptor-like PTPs (CD45, PTPα and PTPγ), both containing one or two catalytic domain(s) of approximately 240 amino acids. The DSPs (VH1-like enzymes) are the most diverse group in terms of substrate specificity and can be distinguished by their ability to hydrolyze pSer/pThr as well as pTyr residues and non-protein substrates, such as inositol phospholipids. The DSP family contains, amongst others, highly specialized types of phosphatases. For instance, members of this family include mitogen-activated protein kinases phosphatases (MKPs), members of the myotubularin family, RNA triphosphatases, and PTEN (phosphatase and tensin homologue deleted on chromosome 10) type phosphatase (Alonso et al., 2004; Wishart and Dixon, 2006).
- Class II cysteine-based PTPs are especially common in bacteria and enzymes of this class appear to be more ancient than class I PTPs. In humans this class is represented by an 18 kDa tyrosine-specific low M_r phosphatase (LMPTP). LMPTP is able to

dephosphorylate tyrosine kinases and their substrates but its biological functions remain unclear. The correlation between expression and activity of variants of this PTP with some human diseases, including cancer, indicates that this phosphatase may be involved in pivotal processes in cell physiology (Malentacchi et al., 2005).

- Class III cysteine-based PTPs are tyrosine/threonine specific phosphatases and probably evolved from a bacterial rhodanese-like enzyme. In humans, this class is represented by the group of Cdc 25 phosphatases: Cdc25A, Cdc25B and Cdc25C. These three cell cycle regulators act by dephosphorylation of Cdks at their inhibitory N-terminal phosphor-Thr/Tyr motifs, a reaction that is required for the activation of these kinases to drive progression of the cell cycle (Hoffman et al., 2004; Kristjansdottir and Rudolph, 2004).
- The fourth class of PTPs is represented by aspartate-based PTPs, which use a different catalytic mechanism with a key aspartic acid and dependence on a cation (Rayapureddi et al., 2003).

PTP family	**Members**
Class I cys-based	Receptor PTP CD45, RPTPμ, RPTPκ, RPTPρ, RPTPλ, RPTPσ, RPTPδ, RPTPα, RPTPε, RPTPγ, RPTPξ, RPTPβ, DEP1, SAP1, GLEPP, PTPS31, PCPTP, STEP, IA2 and IA2β Nonreceptor PTP PTP1B, TCPTP, PTP-MEG2, HePTP, STEP, LYP, PTP-PEST, PTP-HSCF, Typ-PTP and HD-PTP MPKs PAC-1, MKP1, MKP2, MKP3, MKP4, VH3, VH5, PYST2, MKP5, MKP7 and MK-STYX Atypical DSPs VHR, PIR1, BEDP, TMDP, MKP6, DSP20, SKRP, DSP21, MOSP, MGC1136, VHZ, FMDSP, VHX, VHY, HYVH1, VHP, Laforin, RNGTT and STYX PRLs PRL1, PRL2 and PRL3, CDC14s CDC14A, CDC14B, KAP and PTP9Q22 Slingshots SSH1, SSH2 and SSH3 PTENs PTEN, TPIP, TPTE, tensin and C-1-TEN Myotubularins MTM1, MTMR1, MTMR2, MTMR3, MTMR4, MTMR5, MTMR6, MTMR7, MTMR8, MTMR9, MTMR10, MTMR11, MTMR12, MTMR13 and MTMR14
Class II cys-based	LMWPTP
Class III cys-based	CDC25A, CDC25B and CDC25C
Class IV asp-based	EyA1, EyA2, EyA3 and EyA4

Alonso et al., 2004; Souza et al., 2009.

Table 1. Classification of protein tyrosine phosphatases based on amino acid sequences of the catalytic domains

2.2 Mechanisms of PTP catalysis

Different experimental approaches, such as X-ray crystallography, directed site mutagenesis and circular dichroism, have contributed to our understanding of catalysis and substrate recognition by PTPs. Although PTPs have conserved catalytic domains and share a common mechanism of action, substrate specificity of individual PTPs may display substantial specificity, thus resulting in these enzymes to regulate highly specialized and often fundamentally important processes.

The PTP family shares a strictly conserved active site comprising the "P-loop" residues (H/V)**C**(X)$_5$**R**(S/T) and a conserved acidic residue (Denu et al., 1996; Fauman et al., 1996; Zhang 2003; Aoyama et al., 2003). In all structurally characterized PTPs to date, the three-dimensional structure of active-site components is also highly conserved suggesting a common catalytic mechanism. In general, the catalytic site is located in a groove at the protein surface. Its size is responsible for explaining the higher substrate selectivity of classical PTPs (Alonso et al., 2004).

In vitro studies based on model substrates, such as phenyl phosphate or *p*-nitrophenyl phosphate, have provided much of the information on the mechanistic aspects of catalysis. In particular, it is well established that the enzyme completes its action in two major steps. In the first step, the phosphoryl group from the substrate is transferred to the nucleophilic cysteine, forming a phosphoenzyme intermediate. In the second step, this intermediate is hydrolyzed, leading to the regeneration of the enzyme and the release of an inorganic phosphate (Aoyama et al., 2003; Zhang, 1997). Although this two-step mechanism is well-established, some mechanistic aspects still need to be clarified, such as regulatory and inhibitory mechanisms.

3. Protein tyrosine phosphatases and prostate cancer

3.1 LMWPTP

3.1.1 Signaling features

Chernoff and Li (1985) purified a PTP from bovine heart whose characteristics were similar to those described for the low molecular weight acid phosphatase (See item 3.4.1). This low molecular weight (about 18 kDa) protein tyrosine phosphatase (LMWPTP) shares very low sequence homology in relation to the other protein tyrosine phosphatase families, except for the consensus active site motif CX$_5$R, that contains the essential nucleophilic cysteinyl residue, and an identical catalytic mechanism (Tonks, 2006; Tabernero et al, 2008). All PTPs hydrolyze p-nitrophenylphosphate and show inhibition by vanadate, insensitivity to okadaic acid and lack of metal ion requirement for catalysis. LMWPTP contains two conserved adjacent tyrosines, Tyr131 and Tyr132, which are preferential sites for phosphorylation by protein tyrosine kinases and important for the regulation of its activity (Tailor et al, 1997; Buccciantini et al, 1999). This enzyme class is very important in cell signaling processes such as proliferation, adhesion and migration. It can associate with and dephosphorylate many growth factors and receptors, such as platelet-derived growth factor (PDGFR), fibroblast growth factor (FGFR), insulin receptor (IR) and ephrin receptor (Eph), causing downregulation of tyrosine kinase receptor functions and leading to cell division (Souza et al, 2009).

3.1.2 Role in prostate cancer

LMWPTP has been recognized as a positive regulator of tumor growth (Chiarugi et al., 2004). Our research group has a long-standing interest in the possible beneficial prostate cancer biological effects of LMWPTP. In this scenario, we demonstrated that a compound

isolated from the Chilean tree *Persea nubigena* and from the stem bark of *Podocarpus andina* (Podocarpaceae), modulates both expression and activity of LMWPTP in prostate cancer cells (PC3) which was important for diminishing the proliferation ratio of these cells (Bispo de Jesus et al. 2008). More recently, we observed that prostate cancer cells that had LMWPTP silenced showed considerable reduction in invasiveness (unpublished data).
Thus, this enzyme is attracting great interest as a drug target. Zabell et al. (2004) described that specific inhibitors could be rationally designed according to each of the two isoform structures of this class of enzymes. Taddei et al. (2006) observed that, at least in part, the antitumoral activity of Aplidin could be due to the direct oxidation and inactivation of LMWPTP. Marzocchini et al. (2008) reported that the treatment of rats with 1,2-dimethylhydrazine provoked a significant increase in LMWPTP expression in adenocarcinomas, suggesting that this phenomenon is associated with the onset of malignancy.

3.2 SHP-1

3.2.1 Signaling features

Among all members of PTPs, SHP-1 has been suggested as a key signaling protein to control cell growth. Specifically, SHP-1 (an SH2 domain-containing cytosolic PTP) is an important modulator of intracellular phosphotyrosine level in eukaryotic cells, controlling different cell fates, such as proliferation, migration and differentiation through regulating signaling of cytokines such as IL-3R, PDGF- and EGF receptors, and other tyrosine kinase receptors (Tomic et al., 1995; Keilhack et al., 1998). Disruption on SHP-1 regulation can cause abnormal cell growth and induce different kinds of cancers such as leukemia, lymphoma, breast and prostate cancers as well. In order to validate this hypothesis, some authors have inserted the SHP-1 gene into different cancer cell lines and they reported a diminishment on growth of those cells (Zapata et al., 2002). Altogether, these data reinforce that SHP-1 acts as a tumor suppressor protein, regulating cell signaling responsible to growth of eukaryotic cells.

3.2.2 Role in prostate cancer

In men, it is known that androgen deprivation leads to development of a negative growth-regulating loop involving antiproliferative molecules like somatostatin (SST) in prostate adenocarcinoma. Physiologically, SST presents an antiproliferative effect, impairing mitogenic signals upon growth factors signaling (Patel, 1999). The SST signaling starts upon activation of a family of transmembrane receptors (SSTRs), sharing common signaling pathways such as the inhibition of adenylate cyclase, activation of PTP, and modulation of mitogen-activated protein kinase (MAPK). A number of publications support an involvement of SHP- 1 on negative regulation of cellular proliferation by SST (Lahlou et al., 2003). The expression of SHP-1 in rat prostate (Valencia et al., 1997) and in human prostate was shown as well (Tassidis et al., 2010). Despite the limitation of cell culture, some authors have defined SHP-1 as a decisive protein on determining cancer cell phenotype *in vitro* by using two classical prostate cancer cell lines: PC3 and LNCap. They determined an inverse relationship between cell proliferation and secreted somatostain amount. Briefly, SST was able to inhibit both PC-3 and LNCap cell proliferation by an autocrine/paracrine manner, suggesting its participation on blocking cell cycle signaling. Moreover, when SST secretion was blocked, the expression and activity levels of SHP-1 protein were reduced, and PC-3 cell proliferation was increased (Zapata et al., 2002). These authors suggest that SHP-1 could

play a key role in controlling prostatic cell proliferation, which also indicates that SHP-1 expression might be a therapeutic target for treatment of prostate cancer (Zapata et al., 2002). On the other hand, by using human prostate biopsies, Cariaga-Martinez et al. (2009) observed a decrease of SHP-1 and somatostatin in prostate cancer cells, and they demonstrated that this is consistent with aggressiveness of the tumor. In addition, Wu et al. (2003) proposed the diminished or abolished SHP-1 expression could be due to mutation of the SHP-1 gene, methylation of the promoter region or post-transcriptional regulation of SHP-1 protein synthesis. It might also be explained by the action of specific families of miRNAs.

3.3 CDC25

3.3.1 Signaling features

Unbalance on either expression or activity of proteins related to control of cell cycle progression provokes a wide variety of malignant diseases, including prostate cancer. Biochemically, cell cycle progression is a well orchestrated event regulated by well-defined sequential activities of cyclin-dependent kinases (CDKs), cyclins, and other proteins (Karlsson-Rosenthal and Millar, 2006). During mitosis, Cdc2/Cyclin B complexes can be dephosphorylated by the CDC25 phosphatase (a dual-specificity protein tyrosine phosphatase). CDC25 phosphatases play a critical role in regulating cell cycle progression by dephosphorylating CDKs at inhibitory residues and, therefore, have been shown to possess oncogenic potential (Karlsson-Rosenthal and Millar, 2006). In human, CDC25 proteins are encoded by a multigene family: CDC25A, CDC25B, and CDC25C (Turowski et al., 2003). It has been suggested that phosphorylation of CDC25C at Ser216 (activated Chk kinases) negatively regulate the activity of this phosphatase by an immediate cytoplasmic sequestration (Peng et al., 1997). Despite its potential role in prostate cancer, its exact involvement remains unclear.

3.3.2 Role in prostate cancer

Due to its hormone-dependent nature, prostate cancer at the metastatic stage is usually treated with hormone ablation therapy. Androgen receptor (AR) is a ligand-dependent transcription factor and its activity is regulated by numerous AR coregulators. Inadequate incidence of these AR coregulators contributes for the development of prostate cancer. Current studies have shown that AR activity is modulated by phosphorylation at specific sites performed by mitogen-activated protein kinases, Akt/PKB, and cAMP-activated protein kinase A, which control AR transcriptional activity. Guo et al. (2006) reported that AR was tyrosine-phosphorylated in prostate cancer cell lines and that an elevated level of phosphorylation was detected in hormone refractory prostate tumor xenografts, demonstrating that such AR modification may contribute to androgen-independent activation of AR. Chiu et al. (2009) demonstrated for the first time that CDC25A could interact with AR and inhibit its transcriptional activity. Since CDC25A overexpression is implicated in cancer development, their findings may provide an insight into the pathological role of CDC25A and AR in the development of prostate cancer.

In addition, CDC25A phosphatase has been implicated in the regulation of Raf-1 and the MAPK pathway. Raf-1 controls the mitogen activated protein kinase (MAPK) pathway, which has been associated with the progression of prostate cancer to the more advanced and androgen-independent disease. Nemoto et al. (2004) showed that Raf-1 interacts with

CDC25A in PC-3 and LNCap cells and CDC25A inhibitors induced both extracellular signal-regulated kinase (Erk) activation and augmented Raf-1 tyrosine phosphorylation. These results indicate that CDC25A phosphatase regulates Raf-1/MEK/Erk kinase activation in human prostate cancer cells. Indeed, CDC25A controls proliferation and survival signaling, culminating on modulation of prostate cancer progression and aggressiveness.
Moreover, to determine whether CDC25C activity is altered in prostate cancer, Ozen and Ittman (2005) have examined the expression of CDC25C and an alternatively spliced variant in human prostate cancer samples and cell lines. Interestingly, they showed that an active dephosphorylated form of CDC25C was up-regulated in prostate cancer in comparison with normal prostate tissue. In addition, they showed that at the transcriptional level, CDC25C and alternatively spliced variants were both overexpressed in prostate cancer. Finally, their findings suggest that expression of the spliced variants is correlated with biochemical recurrence.
Regarding CDC25B, Ngan et al. (2003) described that its overexpression is associated with the stage of prostate cancer, transiting from a hormone-dependent to a hormone-independent state and contributing to prostate cancer development and progression.

3.4 Acid phosphatase

3.4.1 Signaling features

Acid phosphatases (EC 3.1.3.2), enzymes that catalyze the hydrolysis of a wide range of orthophosphate monoesters, are largely distributed in nature and have been studied in numerous organisms and tissues (Granjeiro et al, 1997; Ferreira et al, 1998a, 1998b; Granjeiro et al, 1999; Fernandes et al, 2003; Jonsson et al, 2007). The enzyme found in mammalian tissues occurs in multiple forms that differ in regard to molecular mass, substrate specificity and sensitivity to inhibitors (Granjeiro et al, 1997). Low relative molecular mass (Mr) enzymes (Mr < 20.0 kDa) are insensitive to tartrate and fluoride and strongly inhibited by SH-reacting compounds. High Mr acid phosphatases (Mr > 100.0 kDa) are inhibited by tartrate and intermediary Mr enzymes (30.0 kDa < Mr<60.0 kDa) by fluoride. In contrast to high Mr acid phosphatases, low Mr enzymes present more restricted substrate specificity, preferentially hydrolyzing p-nitrophenylphosphate, flavin mononucleotide and tyrosine-phosphorylated proteins.
In 1985, Chernoff and Li reported several similarities between the low molecular weight acid phosphatase and one class of protein tyrosine phosphatase (PTP), the low molecular weight protein tyrosine phosphatase (LMWPTP).
The phosphatidic acid phosphatase (PAP) is a key enzyme in both glycerolipid biosynthesis and cellular signal transduction. It was observed that the plasma membrane-bound type 2 PAP, now known as lipid phosphate phosphatase, participates in germ cell migration, epithelial differentiation and other signaling processes (Kanoh et al, 1997; Brindley and Pilquil, 2009).

3.4.2 Role in prostate cancer

Altered acid phosphatase activities can be related to several pathological processes, such as those involving infectious, inflammatory or tumoral processes. For instance, high and intermediary molecular weight acid phosphatases levels are increased in the serum of patients with prostate carcinoma (Hudson et al. 1955), of patients suffering from spleen disorders (Kumar and Gupta, 1971), of patients with endothelial reticulum leukemia (Ketcham et al, 1985), etc.

Human prostatic acid phosphatase has been used as a valuable marker for prostate cancer, before the evaluation by the prostate-specific antigen (PSA). Increased prostatic acid phosphatase serum levels are well correlated with metastatic prostate cancer (Ahmann and Schifman, 1987). In normal human prostate epithelial cells, human prostatic acid phosphatase expression is very high and guarantees the slow proliferation rate of those cells (Goldfarb et al., 1986; Veeramani et al, 2005). On the other hand, decreased activity of this phosphatase correlates with the poor differentiation of high-grade prostate cancer. One possible mechanism by which this phosphatase regulates the proliferation of prostate cancer is due to the dephosphorylation of the receptor HER-2. Uncontrolled phosphorylation of HER-2 leads to increased hormone-refractory growth of prostate cancer cells (Chuang et al, 2010).

3.5 PTEN

3.5.1 Signaling features

PTEN is a tumor suppressor protein, acting as a dual-specificity protein phosphatase. It is one of several enzymes with the ability to dephosphorylate tyrosine-, serine- and threonine-phosphorylated residues (Pulido & van Huijsduijnen, 2008). It also presents lipid phosphatase activity, mainly towards phosphatidylinositol-3,4,5-triphosphate (Maehama & Dixon, 1998). This is crucial to its tumor suppressor function, since it opposes the survival and proliferative actions of many growth factors (Uzoh *et al.*, 2008).

PTEN was first described in 1997. Mutations in its encoding gene were detected, at the time, in several human cancer tissues and cell lines, including prostate cancer (Li *et al.*, 1997). Its loss has been associated mainly with activation of the PI3K/Akt/mTOR pathway, leading to proliferation and survival of cancer cells (Hollander *et al.*, 2011).

3.5.2 Role in prostate cancer

The lack of PTEN has been implicated in the resistance of prostate cancer cells to conventional chemo- and radiotherapy, as well as androgen-independence (Uzoh *et al.*, 2008; Huang *et al.*, 2001; Priulla *et al.*, 2007; Anai *et al.*, 2006; Shen & Abate-Shen, 2007). In a mouse model of prostate cancer, PTEN inactivation was shown to induce growth arrest through the p53-dependent cellular senescence pathway both *in vitro* and *in vivo* (Chen *et al.*, 2005).

Chemo- and radiotherapy resistance is linked to overexpression of Bcl-2, an anti-apoptotic protein that blocks PTEN-mediated apoptosis. Huang *et al.* showed this overexpression to be related to PTEN-loss, as well as establishing an association between PTEN-induced chemosensitivity and inhibition of Bcl-2 expression (Huang *et al.*, 2001).

mTOR inhibition has also been shown to sensitize Pten-null prostate cancer cells to chemo- and radiotherapy (Grunwald *et al.*, 2002; Cao *et al.*, 2006), pointing to PTEN's role in resistance. Interestingly, Cao and colleagues used an mTOR inhibitor other than rapamycin (RAD001 - everolimus) to enhance the cytotoxic effects of radiotherapy on two prostate cancer cell lines (PC-3 and DU145). They found that the increased susceptibility to radiation presented by both cell lines was due to autophagy, instead of apoptosis. They also showed that blocking apoptosis with caspase inhibition and Bax/Bak small interfering RNA leads to the same effects (Cao *et al.*, 2006). TORC1/TORC2 inhibition in association with docetaxel and cisplatin also led to promising results in mice with chemoresistant prostate cancer (Gravina *et al.*, 2011).

PTEN loss effects also extend to the androgen receptor (AR) activity, associated to androgen-independence. AR is shown to be inhibited by PTEN through blockage of the Akt pathway (Shen & Abate-Shen, 2007; Nan *et al.*, 2003). However, a recent study points to the opposite activities of AR and PI3K signaling pathways and their cross-regulation, with inhibition of one activating the other, maintaining cancer cell survival by distinct means. Through combined pharmacological inhibition of both pathways, the authors could achieve near-complete prostate cancer regressions in a PTEN-deficient murine model and in human xenografts (Carver *et al.*, 2011).

Recent studies have also implicated PTEN loss in chemokine receptor 4 (CXCR4)- mediated prostate cancer progression and metastasis, as well as showing that reactive oxygen species (ROS) can increase this outcome through direct inactivation of PTEN by active site oxidation (Chetram *et al.*, 2011).

3.6 DUSP

3.6.1 Signaling features

Dual-specificity phosphatases (DUSPs) are enzymes able to dephosphorylate both tyrosine and serine/threonine residues within their substrate (Patterson *et al.*, 2009). There are 49 gene products characterized as human DUSPs in the Gene Ontology database (The Gene Ontology Consortium, 2000). These are divided into subgroups, according to their substrate specificity. MKPs, one of the best-characterized subgroups, are able to dephosphorylate mitogen-associated protein kinases (MAPKs), which are in turn increasingly implicated in the development and progression of several cancers, including prostate cancer. Another subgroup is named atypical DUSPs. Some of them also show a preference for MAPKs as substrates, but, unlike MKPs, they are mostly of low-molecular mass and lack the N-terminal CH2 (Cdc25 homology 2) domain (Patterson *et al.*, 2009).

In spite of some clear links between some DUSPs, their substrates and specific cancer types, there is still variability in respect to their role in distinct tissue environments. The existing reports regarding prostate cancer are diverse, sometimes even antagonistic. Thus, the precise role of DUSPs in carcinogenesis remains to be clarified (Arnoldussen & Saatcioglu, 2009).

DUSP1 is a member of the MKP group. It is able to dephosphorylate all members of the MAPK family, although displaying preference for p38 and JNK substrates (Magi-Galluzzi *et al.*, 1997; Sun *et al.*, 1993; Franklin & Kraft, 1997).

DUSP3 is an atypical dual-specificity phosphatase that has controversial substrate specificity. ERK 1/2 and JNK were identified as direct substrates for DUSP3 (Todd *et al.*, 1999; Todd *et al.*, 2002), although a later report points to ERK2 as an unlikely substrate for DUSP3 (Zhou *et al.*, 2002). STAT5 was also identified as a substrate for DUSP3 (Hoyt *et al.*, 2007).

DUSP10 is a MKP with preference for p38 and JNK rather than ERK as substrates. It has been implicated in the regulation of innate and adaptive immune responses (Zhang *et al.*, 2004) and also has been shown to have a potent anti-inflammatory activity in prostate cells (Nonn *et al.*, 2007).

DUSP18 is a member of the atypical subgroup of dual-specificity phosphatases whose mRNA expression was identified in several cancer tissues and cell lines, including prostate, among others (Patterson *et al.*, 2009; Wu *et al.*, 2006). It presents phosphatase activity against ERK, JNK and p38 synthetic substrates, with a preference for ERK and JNK (Hood *et al.*, 2002).

3.6.2 Role in prostate cancer

DUSP1 mRNA was found to be overexpressed in the early phases of prostate cancer, but this did not prevent high ERK-1 expression (Loda *et al.*, 1996). Overall, ERK appears to increase DUSP1 expression, decreasing JNK activity and inhibiting apoptosis. In a 2008 study it was shown that coordinate inhibition of AKT/mTOR and ERK-1/MAPK pathways leads to reduced cell growth and proliferation, as well as upregulation of the apoptotic regulator Bcl-2-interacting mediator of cell death (Bim) in a preclinical mouse model of hormone-refractory prostate cancer (Kinkade *et al.*, 2008). Accordingly, a later study showed DUSP1 mRNA expression to be lower in hormone-refractory prostate carcinomas than in benign prostate hyperplasia (BPH) or untreated prostate carcinomas. Higher DUSP1 protein levels were found in BPH, normal prostate and high-grade prostate intraepithelial neoplasia (Rauhala *et al.*, 2005). Consistent with the low levels of DUSP1 in response to androgen ablation, DUSP1 mRNA was found to be upregulated upon androgen treatment of LNCaP cells (Arnoldussen *et al.*, 2008) The androgen receptor (AR) has been identified as responsible for increased expression of DUSP1 (and several other DUSPs) upon interaction with testosterone. However, DUSP1 implication in prostate cancer is not yet fully resolved, since there have been reports showing that both high and low levels of DUSP1 may have an antiapoptotic effect, depending on which MAP kinase DUSP1 is targeting (Rauhala *et al.*, 2005).

Similarly, androgens protect LNCaP cells from 12-O-tetradecanoylphorbol-13-acetate- and thapsigargin-induced apoptosis via down-regulation of JNK activity through an increase in DUSP3 expression. This effect was not observed in androgen-independent DU145 cells (Arnoldussen *et al.*, 2008). Expression analysis in human prostate cancer specimens also show that DUSP3 is increased in prostate cancer compared with normal prostate, evidencing a direct DUSP3 role in prostate cancer progression through JNK-mediated apoptosis inhibition (Arnoldussen *et al*, 2008).

Another DUSP that has been related to prostate cancer is DUSP10. DUSP10 presents anti-inflammatory activity and its expression is increased after treatment with calcitriol, the hormonally active form of vitamin D. This results in the subsequent inhibition of p38 stress kinase signaling and the attenuation of the production of pro-inflammatory cytokines (Nonn, *et al.*, 2006; Krishnan & Feldman, 2010).

4. Concluding remarks

Deciphering the molecular networks that distinguish progressive from non-progressive prostate cancer will bring light on the biology of this tumor, as well as lead to the identification of biomarkers that will aid to the selection of better-suited treatments for each patient. For this, it is crucial to characterize and integrate the molecular mediators involved in prostate cancer biology. In this chapter we pointed out some evidences of the contribution of protein tyrosine phosphatases for prostate cancer pathogenesis. PTPs, as a large enzyme family, can act as prostate cancer suppressors or promoters, depending on their target protein (Table 2). However, studies quantifying PTPs on gene and protein levels in prostate cancer have been limited. New efforts to raise this kind of combinatory data might reveal a spectacular relationship between genotype and PTP activity levels and lead to an understanding of the fundamental role of this enzyme family in controlling malignant cell transformation. This, in turn, may open new avenues to treat prostate cancer based on PTP activity modulation.

Phosphatase	Prostate cancer cell localization	Main action	Main targets in prostate cancer
LMWPTP	cytosol	cancer promoter	unknown
SHP-1	cytosol	cancer suppressor	IL-3R, PDGF- and EGF receptors
CDC25B and CDC25C	nucleus	cancer promoter	unknown
CDC25A	nucleus	cancer suppressor	Androgen receptor (AR)
Acid phosphatase	cytosol	cancer suppressor	Her-2
PTEN	cytosol and nucleus	cancer suppressor	phosphatidylinositol-3,4,5-triphosphate
DUSP	nucleus	cancer promoter	JNK, p38 and ERK

Table 2. Prostate cancer protein tyrosine phosphatases

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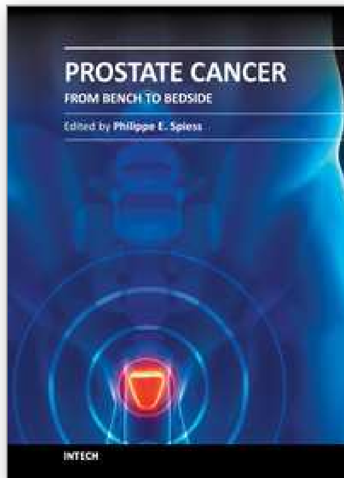

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The present textbook highlights many of the exciting discoveries made in the diagnosis and treatment of prostate cancer over the past decade. International thought leaders have contributed to this effort providing a comprehensive and state-of-the art review of the signaling pathways and genetic alterations essential in prostate cancer. This work provides an essential resource for healthcare professionals and scientists dedicated to this field. This textbook is dedicated to the efforts and advances made by our scientific community, realizing we have much to learn in striving to some day in the not too distant future cure this disease particularly among those with an aggressive tumor biology.

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