Ubiquitin specific peptidases and prostate cancer

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Protein ubiquitination is an important post-translational modification mechanism, which regulates protein stability and activity. The ubiquitination of proteins can be reversed by deubiquitinating enzymes (DUBs). Ubiquitin-specific proteases (USPs), the largest DUB subfamily, can regulate cellular functions by removing ubiquitin(s) from the target proteins. Prostate cancer (PCa) is the second leading type of cancer and the most common cause of cancer-related deaths in men worldwide. Numerous studies have demonstrated that the development of PCa is highly correlated with USPs. The expression of USPs is either high or low in PCa cells, thereby regulating the downstream signaling pathways and causing the development or suppression of PCa. This review summarized the functional roles of USPs in the development PCa and explored their potential applications as therapeutic targets for PCa.

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8   **Abstract**

9   Protein ubiquitination is an important post-translational modification mechanism, which

10   regulates protein stability and activity. The ubiquitination of proteins can be reversed by

11   deubiquitinating enzymes (DUBs). Ubiquitin-specific proteases (USPs), the largest DUB

12   subfamily, can regulate cellular functions by removing ubiquitin(s) from the target proteins.

13   Prostate cancer (PCa) is the second leading type of cancer and the most common cause of

14   cancer-related deaths in men worldwide. Numerous studies have demonstrated that the

15   development of PCa is highly correlated with USPs. The expression of USPs is either high or

16   low in PCa cells, thereby regulating the downstream signaling pathways and causing the

17   development or suppression of PCa. This review summarized the functional roles of USPs in the

18   development PCa and explored their potential applications as therapeutic targets for PCa.

19   **Keywords:** ubiquitin-specific proteases (USPs), deubiquitination, prostate cancer

20   **INTRODUCTION**

21   Regulation of gene expression is a complex process, involving interactions among DNA, RNA,

22   proteins, and environment. The regulatory process of gene expression occurs at multiple levels to

23   maintain the optimal levels of RNAs and proteins (Tran & Hutvagner 2013). As an important

24   regulatory mechanism, post-translational modifications (PTMs) are essential for cellular

25   activities. There are several types of PTMs, such as phosphorylation, acetylation, methylation,

26   sumoylation, and ubiquitination; each of them corresponds to one or more specific functions

27   (Millar et al. 2019).

28   The ubiquitination of proteins plays a very important role in regulating protein function

29   (Komander & Rape 2012). It can regulate almost all aspects of cellular physiology (Hu et al.

30   2021). Ubiquitin, discovered in the 1980s (Cappadocia & Lima 2018), is an 8.5-kDa small

31   protein, containing 76 amino acids. This protein can be post-translationally attached to the

32   substrate protein, usually at a lysine residue (Clague et al. 2015; Rennie et al. 2020). As shown in

33   Figure 1, ubiquitin can covalently conjugate to the substrate proteins by three different enzymes,

34   including E1, E2, and E3, during ubiquitination (Clague et al. 2015). In eukaryotes, the

35   ubiquitin-proteasome system, which is mainly composed of ubiquitin molecules, ubiquitylating

36   enzymes, and 26S proteasomes, is an important pathway for the degradation of damaged or

37   misfolded proteins (Chauhan et al. 2021; Svikle et al. 2022).

38   Ubiquitination is a covalent modification, which can be reversed by deubiquitinating

39   enzymes (DUBs) (Bhoj & Chen 2009; Chen et al. 2021a). DUBs are proteases, which cleave

40   peptide or isopeptide bonds between the two linked ubiquitin molecules or between ubiquitin and

41   modified proteins (Clague et al. 2019). It can reverse the E3 ubiquitin ligase-mediated protein

42   modifications (Cheng et al. 2019b), thereby protecting proteins from degradation by the

43   proteasomes (Haq et al. 2018). Similar to ubiquitination, deubiquitination, catalyzed by DUBs,

44   also plays a critical role in regulating cell functions (Schmidt et al. 2005; Daniel & Grant 2007;

45   Kennedy & D'Andrea 2005; Lai et al. 2020; Ramakrishna et al. 2011; Ramakrishna et al. 2015).

46   Recently, numerous DUBs have shown correlations with many diseases, such as cancer,

47   inflammatory diseases, diabetes, and neurodegenerative diseases (Chen et al. 2021a; Leznicki &

48 Kulathu 2017). The human genome encodes more than 100 DUBs, most of which are cysteine

49 proteases (Leznicki & Kulathu 2017). DUBs are divided into six families, including ubiquitin-

50 specific proteases (USPs), ubiquitin C-terminal hydrolases (UCHs), ovarian tumor-related

51 proteases (OTUs), Machado-Joseph disease protein domain proteases (MJDs), motif interacting

52 with Ub-containing novel DUB family (MINDYs), and zinc finger-containing ubiquitin

53 peptidase 1 (ZUP1) (Harrigan et al. 2018; Kwasna et al. 2018; Lei et al. 2021). USPs are the

54 largest subfamily of DUBs, which are closely correlated with the development and progression

55 of numerous cancer types, such as colorectal cancer (CRC) (Li et al. 2020), prostate cancer (PCa)

56 (Liao et al. 2021a), liver cancer (Du et al. 2021), and breast cancer (Ma et al. 2019). Moreover,

57 several USPs can also inhibit the occurrence and progression of cancer, such as glioblastoma

58 (Kit Leng Lui et al. 2017).

59   PCa is the second leading type of cancer and the most common cause of cancer-related

60 deaths in men worldwide (Vietri et al. 2021). The therapeutic strategies for PCa have been

61 improved, albeit modestly, in the past few years, increasing the overall survival times of PCa

62 patients (Nag & Dutta 2020). PCa is highly dependent on androgen receptor (AR) signaling. AR

63 is important for the growth and differentiation of normal prostate cells and plays a key role in the

64 pathogenesis of PCa (Smolle et al. 2017). Therefore, androgen deprivation therapy (ADT) is the

65 main treatment option for metastatic PCa (mPCa) (Sena & Denmeade 2021; Tsujino et al. 2021).

66 Despite its effectiveness, the patients receiving ADT can develop resistance, eventually

67 developing castration-resistant PCa (CRPCa) (Fujita & Nonomura 2019). Abiraterone and

68   enzalutamide are second-generation ADTs, which are used for the treatment of CRPCa;

69   however, cancer also eventually progresses to metastatic CRPCa (mCRPCa) (Berish et al. 2018).

70   In addition to AR, the loss of tumor suppressors and aberrant activation or expression of

71   oncogenes also play a crucial role in the progression of PCa. For example, the tumor suppressor

72   genes *p53* and *PTEN* and oncogene *Myc* are involved in the development and progression of PCa

73   (Logothetis et al. 2013; Whitlock et al. 2020). In addition, numerous studies have also shown a

74   strong correlation between the expression of DUBs and the progression of PCa (Deng et al.

75   2021; Ge et al. 2021; Jin et al. 2018; McClurg & Robson 2015; Peng et al. 2022).

76   Ubiquitination and deubiquitination can regulate various aspects of human cell biology and

77   physiology. The malfunction of these modifications can cause numerous diseases, including

78   cancers. There has been a growing interest in exploiting the components of ubiquitination and

79   deubiquitination machinery as therapeutic targets. Due to their greater numbers and diversity,

80   DUBs are intrinsically attractive as potential drug targets. More than half of the total DUBs are

81   USPs, which are cysteine peptidases. Currently, USPs have been extensively studied in various

82   types of cancer. In terms of USPs' role in PCa, Islam et al. showed that targeted ubiquitinase

83   could regulate the therapeutic pathways of PCa (Islam et al. 2019). This review article

84   summarized the expression patterns of different USPs in PCa and correlations between these

85   expression patterns and the overall survival times of PCa patients as well as highlighted the

86   mechanism of USPs, regulating the development and progression of PCa. This review article

87   might provide basic knowledge for general readers as well as cancer researchers, especially those

88 who are dedicated to PCa research and developing PCa drug targets.

SURVEY METHODOLOGY

90 PubMed database was used for related literature search using the keyword "USP," "ubiquitin

91 specific peptidase," "ubiquitin-proteasome system," "ubiquitination," "deubiquitination,"

92 "prostate cancer," and "cancer."

STRUCTURAL CHARACTERISTICS OF USPs

94 USPs were first discovered and cloned in *Saccharomyces cerevisiae* (Tobias & Varshavsky

95 1991). They are the largest subfamily of DUBs having a total of 58 members. The number of

96 USPs has increased since the evolution of E3 ubiquitin ligases (Semple 2003). The size of USPs

97 ranges from 330 amino acids to 3500 amino acids with an average size of 800-1000 amino acids

98 for full-length enzymes. The catalytic structural domain of USPs contains 295-850 amino acids;

99 the catalytic structural domain of 27 USPs contains 300-400 amino acids, while that of 29 USPs

100 contains 400-850 amino acids (Ye et al. 2009). USPs have also other diverse domains in terms of

101 size and structure (Hariri & St-Arnaud 2021). However, there is a high degree of homology

102 within the catalytic domain. The catalytic core of USPs contains three motifs, consisting of very

103 conserved catalytic Cys residues, catalytic His residues, and catalytic Asp/Asn residues, which

104 form the catalytic triad (Nijman et al. 2005; Ye et al. 2009). In addition to the catalytic domain,

105 USPs also have domains for subcellular localization, substrate specificity, zinc binding, and

106 ubiquitin recognition (Hariri & St-Arnaud 2021; Nijman et al. 2005; Ye et al. 2009). Figure 2A

107 shows USP4, USP7, USP14, USP19, and USP44 as examples of USPs having major domains.

108   The ubiquitin-like (UBL) domain of USPs can regulate their catalytic activity; however, the

109   mechanism of action of the UBL domain in each USP varies. For example, the UBL domain of

110   USP14 is important for its localization on proteasome and might enhance its catalytic capability.,

111   while that of USP4 binds to the catalytic domain, showing a competitive relationship with

112   ubiquitin. As shown in Figure 2B, the UBL4 and UBL5 domains of USP7 are located on its C-

113   terminal and can affect its deubiquitinating activity by promoting conformational changes and

114   facilitating the formation of a catalytic center (Faesen et al. 2012).

115   Different USPs have specific substrate proteins; therefore, they can regulate different

116   signaling pathways (Ye et al. 2009). USPs can stabilize various oncoproteins or alter their

117   cellular localization by deubiquitination, which can cause the development and progression of

118   cancer (Chauhan et al. 2021). Numerous studies have shown that targeting USPs might be a

119   promising therapeutic approach for cancer treatment (Dai et al. 2020; Du et al. 2021; Li et al.

120   2020; Ma et al. 2019; Nininahazwe et al. 2021; Zhu et al. 2020).

121   **USPs AND PCa**

122   **USP1**

123   The mRNA expression levels of *USP1* were higher in the PCa tissues as compared to those in the

124   normal tissues. However, there were no differences in protein expression levels between PCa and

125   normal tissues. USP1 could promote the proliferation of PCa cells, while the knockdown of the

126   *USP1* gene led to the inhibition of cellular proliferation (Liao et al. 2021a). Therefore, USP1

127   might play a promotional role in the development of PCa. Moreover, USP1 was highly expressed

128   in cancer and was strongly correlated with the poor prognosis of patients with numerous cancer

129   types, such as liver cancer, breast cancer, and multiple myeloma (Das et al. 2017; Liao et al.

130   2021b; Ma et al. 2019). These studies further supported USP1 as a potential target for cancer

131   therapy. USP1 activity can be regulated by binding to UAF1 (USP1 associated factor 1), a

132   protein, which contains a WD40 repeat sequence (Cohn et al. 2007). This binding significantly

133   increases the enzymatic activity of USP1 (Cohn et al. 2007; García-Santisteban et al. 2013). The

134   KDM4A (histone demethylase lysine-specific demethylase 4A) is upregulated in PCa, which is

135   crucial for the survival and growth of PCa cells (Cui et al. 2020). USP1 can promote the growth

136   and tumorigenesis of PCa cells by stabilizing the expression of KDM4A (Cui et al. 2020).

137   The SIX1 (sine oculis homeobox homolog 1) is a poor prognostic indicator in PCa. USP1 can

138   interact with SIX1 and stabilize its protein levels in a GRP75 (glucose regulated protein 75)-

139   dependent manner, thereby promoting the cellular proliferation and castration resistance of PCa

140   (Liao et al. 2021a; Liao et al. 2022).

141   **USP2**

142   USP2 is an oncoprotein overexpressed in PCa tissues (Priolo et al. 2006). USP2a is the largest

143   isoform of USP2 (Renatus et al. 2006). Priolo et al. found that USP2a could protect the PCa cells

144   from apoptosis, and its overexpression showed a tumorigenic effect in mice (Priolo et al. 2006).

145   In addition, the overexpression of USP2a can also enhance the proliferation and aggressiveness

146   of PCa cells (Benassi et al. 2012). Studies have shown that the mRNA and protein expression

147   levels of USP2a are upregulated in hepatocellular carcinoma (Xiong et al. 2021). USP2a can

148   significantly promote the growth, invasion, and metastasis of liver cancer cells and is positively

149   correlated with poor pathological grading, lymphatic metastasis, and poor prognosis (Xiong et al.

150   2021). Therefore, it can be speculated that USP2a might be a potentially effective target for

151   cancer therapy. The upregulation of USP2 increases the levels of deubiquitinated substrates. For

152   example, USP2 can stabilize the protein levels of FAS (fatty acid synthase), MDM2 (murine

153   double minute 2), cyclin D1, and Aurora-A (Chuang et al. 2018). These proteins might play a

154   critical role in the development and progression of PCa. Myc is an oncoprotein; its

155   overexpression contributes to the development of PCa. USP2a can indirectly upregulate the

156   expression of Myc to regulate the MDM2-p53-miR-34b/c axis by promoting the progression of

157   cancer (Benassi et al. 2012; Benassi et al. 2013; Nelson et al. 2012). Fatty acid synthase (FAS) is

158   overexpressed in prostate cancer, and it can protect the cancer cells from apoptosis (Graner et al.

159   2004). USP2a can promote the development of PCa by stabilizing FAS and preventing its

160   proteasomal degradation. Seelan et al. suggested that USP2 could deubiquitinate acid ceramidase

161   (ACDase) in the LNcap cell, and the protein expression levels of ACDase were highly correlated

162   with USP2. Studies also showed that the mRNA and protein expression levels of ACDase were

163   upregulated in the PCa cells (Seelan et al. 2000). The overexpression of ACDase could promote

164   the proliferation of PCa cells *in vitro* and *in vivo* (Mizutani et al. 2015).

165   **USP4**

166   Studies have shown that USP4 has lower protein and mRNA expression levels in PCa tissues as

167   compared to those in normal tissues (Chen et al. 2021b). Therefore, it can be speculated that

168 USP4 might be a potentially effective target for the treatment of PCa. In PCa, METTL3

169 (methyltransferase like 3) is an upstream negative regulatory molecule of USP4. The

170 upregulation of METT3 levels leads to the downregulation of USP4 levels, thereby reducing its

171 deubiquitination ability, which causes a reduction in the levels of ELAVL1 (ELAV like RNA-

172 binding protein 1). Consequently, the reduction in the ELAVL1 levels increases the expression

173 levels of ARHGDIA (Rho GDP dissociation inhibitor α), which promotes the migration and

174 invasion of PCa cells. It has been shown that the mRNA and protein expression levels of

175 ARHGDIA are upregulated in PCa cells. In addition, the survival curve analysis showed a much

176 shorter relapse-free survival of the PCa patients with higher *ARHGDIA* mRNA expression levels

177 (Chen et al. 2021b). Therefore, it can be concluded that the invasion and metastasis of PCa cells

178 can be inhibited by targeting and increasing the expression level of USP4.

179 **USP7**

180 USP7 is also known as herpesvirus-associated ubiquitin-specific protease (HAUSP) (Pozhidaeva

181 et al. 2015). It has been overexpressed in PCa cells and is correlated with the invasion of their

182 cells (Song et al. 2008). It can affect the migration, invasion, and sphere formation in PCa cells

183 (Lee et al. 2020). The knockdown of the *USP7* gene can reduce the proliferation of PCa cells and

184 induce their apoptosis (Shin et al. 2020). The PCa patients with high expression of *USP7* had a

185 worse prognosis in a large clinical population (Park et al. 2021). USP7 can interact with multiple

186 substrate proteins, such as AR, FOXA1, FOXO4, PTEN, PLK1, MDM2, and CCDC6, to

187 stabilize their protein levels (Chen et al. 2015; Morra et al. 2017; Park et al. 2021; Peng et al.

188 2019; Song et al. 2008; van der Horst et al. 2006; Weinstock et al. 2012). USP7 is positively

189 correlated with the PLK1 expression; both the USP7 and PLK1 have strong clinical relevance

190 and are correlated with the poor prognosis of patients (Shin et al. 2020). The tissue expression

191 levels of CCDC6 and USP7 can be used as markers to assess the treatment effects of advanced

192 PCa, and their high expression predicts poor prognosis in patients with advanced PCa (Morra et

193 al. 2017).

194 **USP9X**

195 USP9X, a conserved DUB, has a downregulated expression level in PCa tissues. The depletion

196 of USP9X promotes the proliferation, migration, and invading abilities of PCa cells; these

197 invasion and migration abilities are greater than the proliferation ability. Zhang et al. showed that

198 the downregulation of the USP9X expression was correlated with poor differentiation and local

199 invasion of PCa (Zhang et al. 2019). This indicated that the PCa with low *USP9X* expression was

200 highly deteriorated and had a negative impact on patients. USP9X can stabilize the levels of

201 various protein substrates, such as PBX1, ERG, and IRS-2 (Furuta et al. 2018; Liu et al. 2019;

202 Wang et al. 2016). PBX1 can promote the proliferation of PCa cells and is highly expressed in

203 PCa. Studies have shown that the increased levels of PBX1 often lead to chemoresistance, which

204 can be overcome in PCa patients by targeting the USP7-PBX1 axis (Liu et al. 2019). ERG is a

205 major driver of PCa. Blocking the development of PCa by knocking down the USP9X leads to

206 the ubiquitination and degradation of ERG protein (Wang et al. 2014).

207 **USP10**

208 The expression level of USP10 is upregulated in PCa tissues as compared to benign prostate

209 tissues. USP10 can promote the proliferation of PCa cells and play an oncogenic role. The high

210 expression of USP10 is correlated with the poor prognosis of patients. USP10 can deubiquitinate

211 and stabilize the protein levels of G3BP2 (GTPase-activating protein-binding protein 2) and

212 inhibit p53 activity to promote AR signaling pathway (Takayama et al. 2018). G3BP2 is

213 upregulated in PCa and might serve as an independent prognostic marker for PCa patients

214 (Ashikari et al. 2017).

215 **USP12**

216 USP12 is a novel biomarker for PCa. Its expression levels were upregulated in PCa and CRPCa.

217 The upregulation of USP12 expression is correlated with the poor prognosis of PCa patients.

218 McClurg et al. found that the PCa patients with high expression levels of USP12 had

219 significantly shorter overall survival and shorter recurrence time (McClurg et al. 2018b). USP12

220 is also closely associated with the levels of proliferation marker MCM2. Therefore, it can be

221 inferred that USP12 can promote the proliferation of PCa cells. Mechanistically, USP12 can

222 promote the development of PCa by stabilizing MDM2 protein levels and reducing p53 levels

223 (McClurg et al. 2018b). USP12 is a novel regulator of AR by interacting with Uaf-1 and WDR20

224 to enzymatically perform the deubiquitination of AR, thereby enhancing its stability and

225 transcriptional activity (Burska et al. 2013; McClurg et al. 2014). On the other hand, USP12 can

226 also stabilize AR proteins and enhance their transcriptional activity by stabilizing the AKT

227   (protein kinase B) dephosphorylases (PHLPP and PHLPPL) (McClurg et al. 2014). Stabilizing

228   the AR protein and increasing its transcriptional activity can promote the proliferation and

229   survival of PCa cells (Burska et al. 2013).

230   **USP14**

231   USP14 promotes the proliferation of PCa cells and is closely associated with its progression

232   (Liao et al. 2017). It can also promote the development of PCa by stabilizing AR protein and

233   ATF2 (activating the transcription factor 2) (Geng et al. 2020; Liao et al. 2017). USP14 is a

234   novel regulator of AR (Liao et al. 2017). AR protein is overexpressed in PCa and plays a key

235   role in its growth and progression (Liao et al. 2017). *ATF2*, an oncogene of PCa, facilitates the

236   proliferation of PCa cells (Geng et al. 2020).

237   **USP15**

238   The Oncomine public data showed that the expression levels of *USP15* were significantly

239   elevated in PCa tissues, showing its potential clinical significance in PCa (Padmanabhan et al.

240   2018). Studies showed reported that USP15 was highly expressed in various malignancies,

241   including gastric cancer. Moreover, the upregulation of USP15 expression was positively

242   correlated with the clinical features of gastric cancer, such as tumor size, depth of invasion,

243   lymph node involvement, tumor-node-metastasis stage, perineural invasion, and vascular

244   invasion. *USP15* is also strongly associated with poor prognosis of the patient and might be an

245   oncogene in gastric cancer (Zhong et al. 2021). Notably, Fukushima et al. suggested that USP15

246   could inhibit the proliferation of the PCa cell line (PC-3) (Fukushima et al. 2017).

247 Mechanistically, USP15 inhibits the proliferation of PCa cells by antagonizing the NEDD4-

248 induced ubiquitination of IRS-2, which leads to the reduction of tyrosine phosphorylation of

249 IRS-2, resulting in a decreased IGF signaling (Fukushima et al. 2017). The IGF signaling

250 pathway and increase in IGF levels contribute to the proliferation of PCa cells (Ahearn et al.

251 2018).

252 **USP16**

253 The expression level of USP16 is higher in PCa tissues as compared to those in the normal

254 prostate tissues and is correlated with the poor prognosis of PCa patients. USP16 can promote

255 the cellular proliferation and growth of PCa (Ge et al. 2021). c-Myc, an oncoprotein, is involved

256 in cellular proliferation. USP16 can regulate the growth of PCa cells by stabilizing c-Myc (Ge et

257 al. 2021).

258 **USP17**

259 USP17 has higher mRNA and protein levels in PCa tissues as compared to those in normal

260 prostate tissues. The PCa patients with lower expression levels of USP17 have higher overall

261 survival (Baohai et al. 2019). The knockdown of the *USP17* gene can promote the production of

262 ROS to induce apoptosis and decrease p65 phosphorylation, thereby inhibiting the proliferation,

263 migration, and invasion of PCa cells as well as the progression of PCa (Baohai et al. 2019).

264 **USP19**

265 USP19 could regulate the growth of DU145, PC-3, and 22RV1 PCa cell lines but did not affect

266   that of the LNCaP PCa cell line (Lu et al. 2011). The knockdown of the *USP19* gene could

267   inhibit the progression of PCa in two ways; first, by causing defects in cell cycle progression and

268   delaying the progression from G0/G1 to S phase, and second, by accumulating p27^{Kip1} and

269   inhibiting the ability of USP19 to regulate cell growth (Lu et al. 2011).

270   **USP22**

271   USP22 has an important role in promoting malignant phenotypes by enhancing the stability of

272   multiple cancer-associated protein targets through deubiquitination (Schrecengost et al. 2014).

273   The mRNA and protein expression levels of USP22 are significantly upregulated in PCa. *USP22*

274   is a pro-oncogenic factor in PCa. Animal studies showed that USP22 conferred an excessive

275   proliferation phenotype *in vivo* (McCann et al. 2020). USP22 is positively associated with the

276   progression of PCa. Its upregulation not only shortens the survival times of patients but also

277   correlates with the recurrence and poor prognosis of patients (Nag & Dutta 2020). Therefore,

278   USP22 can be used as a diagnostic biomarker. Mechanistically, USP22 promotes the progression

279   of PCa by stabilizing the AR protein levels and regulating the AR-Myc signaling pathway

280   (Schrecengost et al. 2014).

281   **USP25**

282   Although the clinical data showing the exact role of USP25 in PCa is currently lacking, *USP25*

283   expression is downregulated in PCa tissues as compared to normal tissues (Chen et al. 2021b).

284   The wnt/β-catenin pathway is an important pathway for the development and progression of PCa

285   (Cheng et al. 2019a). Tankyrase (TNKS) is a key mediator of the Wnt signaling pathway. USP25

286   can stabilize TNKS protein to promote the proliferation of PCa cells (Cheng et al. 2019a).

287   **USP26**

288   The expression level of USP26 is low in PCa tissues as compared to normal prostate tissues

289   (Wosnitzer et al. 2014). A study reported that the mutations in the *USP26* gene were not

290   involved in the development of PCa, suggesting that the role of USP26 in the development of

291   PCa might be due to changes in its protein expression levels (Dirac & Bernards 2010). USP26 is

292   an AR signaling regulator, which reverses AR ubiquitination, regulates the AR transcriptional

293   activity, and protects the AR proteins from degradation (Dirac & Bernards 2010). USP26 has a

294   cancer promoter role due to its regulatory effects on AR.

295   **USP33**

296   The mRNA and protein expression levels of USP33, also known as VDU1, are upregulated in

297   PCa (Ding et al. 2021; Guo et al. 2020). Guo et al. found that USP33 was an important tumor-

298   promoting factor in PCa. It can inhibit apoptosis and enhance the cell survival of PCa cells (Guo

299   et al. 2020). Current studies have shown that USP33 is an effective target for the treatment of

300   PCa. USP33 promotes the development of PCa through two pathways. First, USP33 interacts

301   with DUSP1 (dual-specificity phosphatase-1) to negatively regulate the JNK (cJUN NH2-

302   terminal kinase) activation, thereby inhibiting the apoptosis of PCa cells (Guo et al. 2020).

303   Second, PCa cells have upregulated levels of circ_ 0057558, which is a new biomarker for PCa

304   and promotes cancer development by regulating the miR-206－USP33－c-Myc axis.

305   Importantly, the expression levels of *USP33* and *circ _ 0057558* are positively correlated with

306   PCa (Ding et al. 2021).

307   **USP34**

308   *USP34* gene is correlated with the recurrence of PCa and is a predictive marker for its recurrence

309   after radical prostatectomy. The high mRNA expression level of *USP34* has a protective effect

310   on the recurrence of PCa. Studies have shown that the Th2 (type 2 T helper) and Tcm (central

311   memory T cell) immune cells are associated with the recurrence of PCa after radical

312   prostatectomy and are the independent recurrence prevention factors. *NDUFA13*, *UQCR11*, and

313   *USP34* are involved in the infiltration of Th2 and Tcm cells in tumor tissues. The high

314   expression of the *USP34* can activate the Th2 and Tcm immune cells and recognize tumor cells

315   through cellular and humoral immune effector mechanisms, thereby delaying the recurrence of

316   PCa and improving prognosis. Conversely, the high expression levels of *NDUFA13* and

317   *UQCR11* can inhibit tumor recognition by the human immune system, thereby significantly

318   increasing the probability of tumor recurrence (Rui et al. 2019).

319   **USP39**

320   PCa cells, especially the AR-negative PCa cells have upregulated expression levels of *USP39*

321   (Huang et al. 2016). USP39 is a biomarker, which predicts poor prognosis and recurrence in

322   patients. Studies have shown that USP39 can affect the colony formation of cancer cells and

323   tumor growth. The inhibition of USP39 can induce G2/M phase arrest and promote apoptosis

324   (Huang et al. 2016). USP39 is positively correlated with EGFR (epidermal growth factor

325   receptor) levels; USP39 upregulates the mRNA and protein expression levels of EGFR (Huang

326   et al. 2016). Studies have shown that EGFR is involved in the bone metastasis of PCa (Thoma

327   2017). Therefore, inhibiting the EGFR signaling pathway might suppress the metastasis of PCa

328   (Xiong et al. 2020). It is speculated that USP39 is a potential target for the treatment of PCa.

329   **USP44**

330   USP44 has a higher protein expression level in malignant and mPCa cells as compared to that in

331   benign and weak mPCa cells (Park et al. 2019). USP44 can promote tumor formation and CSC

332   (cancer stem cell) -like properties of PCa cells. USP44 could promote the invasive and migratory

333   abilities of PCa cells *in vitro*, indicating its oncogenic behavior (Park et al. 2019).

334   Mechanistically, USP44 can deubiquitinate to stabilize the EZH2 (enhancer of zeste homolog 2)

335   protein levels and promote the development of PCa (Park et al. 2019). Moreover, EZH2 could

336   facilitate the proliferation of PCa cells *in vitro* and *in vivo*. The overexpression of EZH2 is

337   correlated with the deterioration of hormone-refractory mPCa. EZH2 is also a risk marker of the

338   lethal progression of PCa (Varambally et al. 2002). Taken together, USP44 plays a role in the

339   progression of PCa by regulating EZH2.

340   **USP46**

341   USP46 has highly similar to USP12 and has overlapping biological functions in PCa (McClurg et

342   al. 2018a). The increased mRNA expression level of *USP46* could predict a shorter relapse-free

343   survival of patients. McClurg et al. found that cancer development could be inhibited by

344   targeting USP46 (McClurg et al. 2018a). Moreover, USP46 can affect the progression of PCa by

345   regulating the AR-AKT-MDM2-p53 signaling pathway (Li et al. 2013; McClurg et al. 2018a).

346   The correlations between USPs and PCa are summarized in Table 1.

347   **CONCLUSIONS**

348   Despite the developments in the treatment of PCa, there is an increasing need for new therapeutic

349   targets. DUBs play an important role in the development of PCa and are promising drug targets.

350   The development of small molecule inhibitors, targeting DUBs, holds great promise for the

351   treatment of PCa. Some inhibitors have been applied in clinical practices, such as b-AP15, ML323,

352   and Spautin-1. However, these studies are very limited and require further investigation. In

353   addition, USPs are correlated with numerous cancer types. Thus, developing effective inhibitors

354   against USPs are a promising method of finding new drugs for the treatment of cancers, including

355   PCa. This review summarized the correlations between USPs and PCa. It was speculated that

356   DUBs, especially USPs, might be effective therapeutic targets, provided that their molecular

357   mechanism in PCa is extensively investigated. Therefore, to develop small molecule inhibitors

358   against USPs for the clinical treatment of PCa and other cancers, more studies regarding the

359   molecular mechanisms of USPs in various cancers and how these USPs themselves are regulated

360   in future.

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Figure 1

Ubiquitination/deubiquitination modifications and their regulatory role in protein degradation and cellular physiological functions.

The process of ubiquitin (ub) binding to substrate proteins in the presence of E1, E2 and E3. This process is reversible and can remove ubiquitination modifications of substrate proteins in the presence of deubiquitinating enzymes (DUB). ubiquitination modifications at position K48 are proteins that undergo degradation to protein fragmentation via the 26S proteasome, while ubiquitination modifications at positions K6, K11, K27, K29, K33, K63 and M1 are involved in the regulation of numerous physiological processes in the cell.

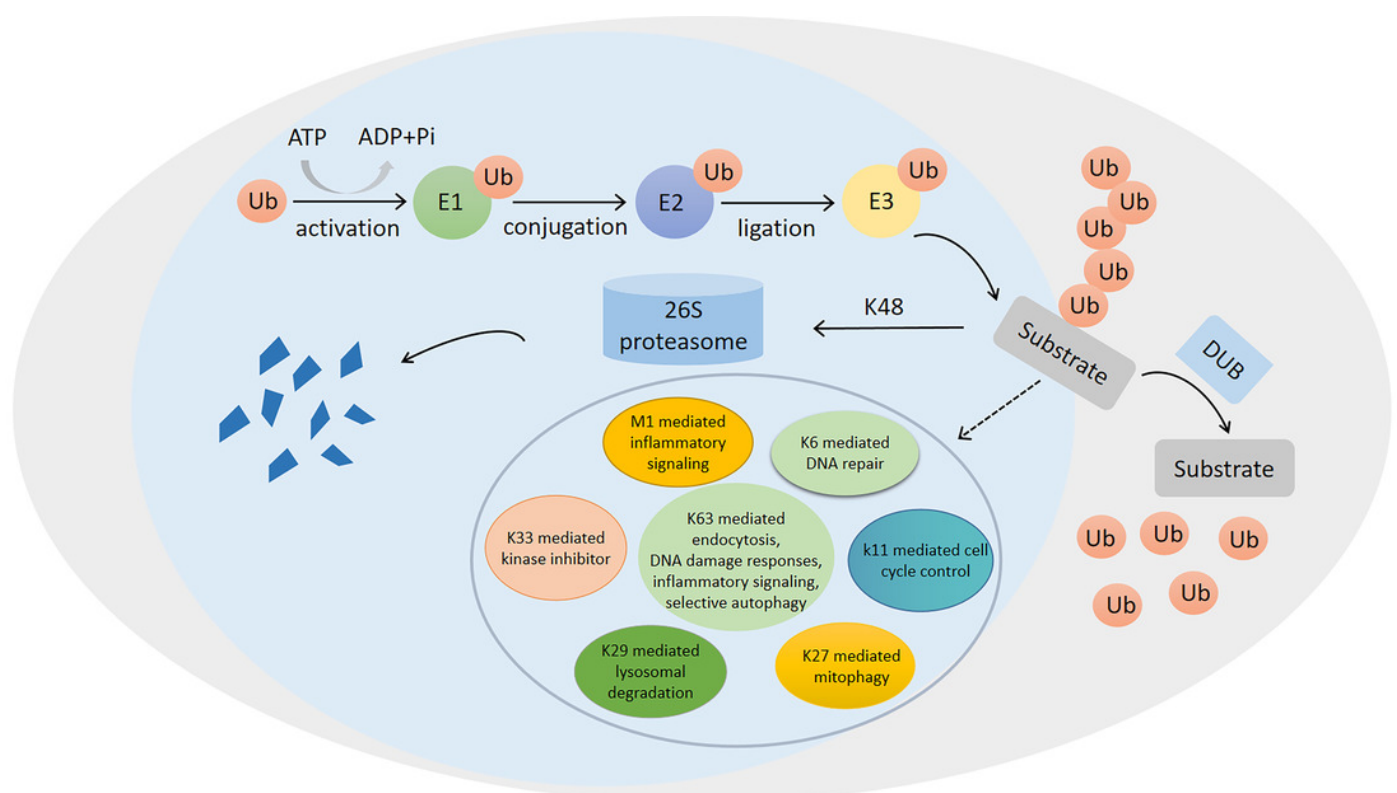
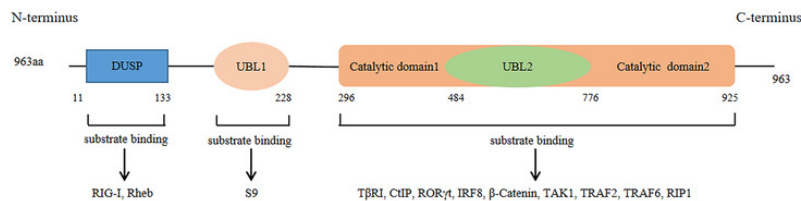
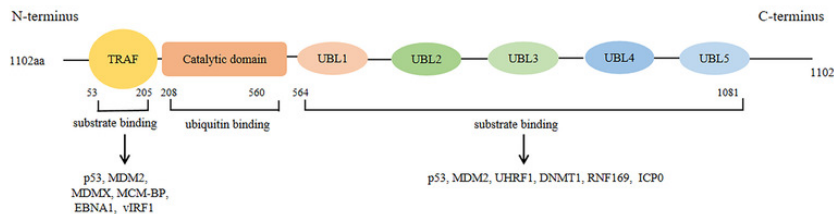
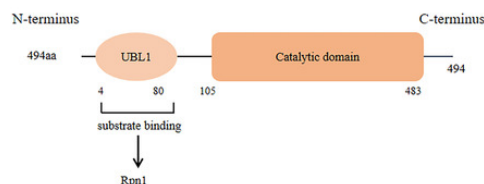
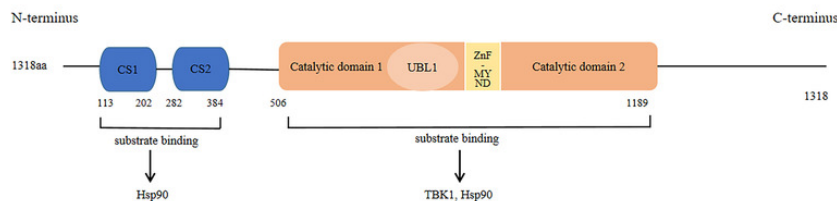



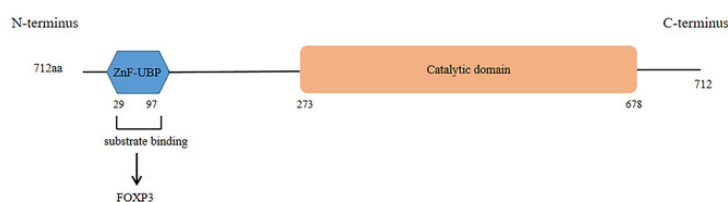
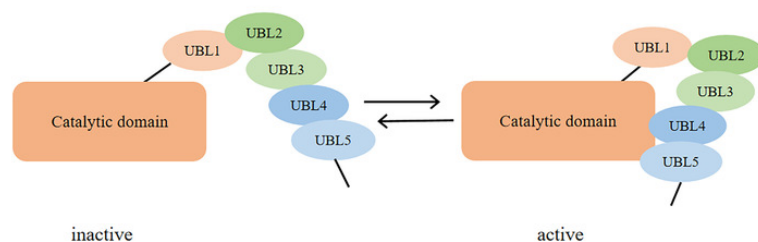
Figure 2

The general domain structure of USP4, USP7, USP14, USP19 and USP44.

(A) The DUSP (domain in USP) domain, UBL (ubiquitin-like) domain, TRAF (tumor necrosis factor receptor associated factor)-like domain, catalytic domain, CS (CHORD and SGT1) domain, ZnF-MYND (zinc-finger myeloid translocation protein 8, Nervy and Deaf1) domain and ZnF-UBP (zinc-finger ubiquitin binding) domain are represented by different colors and shapes. The numbers indicate the amino acid residues. As shown by the arrow, different USP domains bind to different substrate proteins. (B) The 5 UBL domains of USP7 make up the UBL unit. UBL4 and UBL5 interact with the catalytic domain of USP7 to activate USP7; Conversely, inactivation.

A.

USP4

USP7

USP14

USP19

USP44

B.

Ubiquitin-specific peptidases (USPs) related to prostate cancer

1 **Table 1: Ubiquitin-specific peptidases (USPs) related to prostate cancer**

USPs	Expression in prostate cancer	Pathways/Mechanism	Targets	Inhibitors	Reference
USP1	high expression (mRNA)	stabilization of KDM4A protein levels regulation of GRP75-SIX1 signaling axis	KDM4A SIX1	ML323 pimozide	*Liao et al. (2021a);* *Ma et al. (2019);* *García-Santisteban et al. (2013);* *Cui et al. (2020)*
USP2	high expression	regulation of MDM2-p53-Myc signaling axis stabilization of FAS protein levels stabilization of ACDase protein levels	MDM2 FAS ACDase	β-lapachone ML364	*Priolo et al. (2006);* *Nelson et al. (2012);* *Graner et al. (2004);* *Seelan et al. (2000);* *Gopinath et al. (2016);* *Zhang et al. (2021)*
USP4	low expression	regulation of ELAVL1-ARHGDIA signaling axis	ELAVL1	Vialinin A	*Chen et al. (2021b);* *Xu et al. (2021)*
USP7	high expression	stabilization of PLK1 protein levels regulation of MDM2/MDMX-p53 signaling pathway regulation of AR signaling pathway regulation of localization of PTEN	PTEN AR KDM6A MDM2M DMX p53 PLK1	P5091 P22077 Almac4 HBX19818 GNE-6776 Quinazolin-4(3H)-one HBX41108	*Song et al. (2008);* *Shin et al. (2020);* *Peng et al. (2019);* *Chen et al. (2015);* *Li et al. (2002);* *Qi et al. (2020);* *Wang et al. (2021);* *Dai et al. (2020);* *Li et al. (2021);* *Tang et al. (2017)*
USP9X	low expression	regulation of ERG signaling pathway regulation of MMP9-DRP1 signaling axis	ITCH ERG PBX1	WP1130 G9	*Zhang et al. (2019);* *Lu et al. (2019);* *Pal et al. (2018)*
USP10	high expression	regulation of AR singaling pathway	G3BP2	Spautin-1	*Takayama et al. (2018);* *Liao et al. (2019)*
USP12	high expression	regulation of AR signaling pathway regulation of TP53-MDM2-AR-AKT signaling axis regulation of AKT pathway	H2A H2B AR MDM2 PHLPPs	GW7647	*McClurg et al. (2018b);* *McClurg et al. (2014)*

3   Table 1. Continued.

USPs	Expression in prostate cancer	Pathways/Mechanism	Targets	Inhibitors	Reference
USP14	unknow	stabilization of AR and MDM2 protein levels stabilization of ATF2 protein levels regulation of AR signaling	AR MDM2 ATF2	IU1 S5 b-AP15	*Liao et al. (2017);* *Geng et al. (2020);* *Xu et al. (2020);* *Ming et al. (2021)*
USP15	High expression (mRNA)	antagonizing the effect of NEDD4 to regulate IGF signaling pathway	Nedd4	Mitoxantrone USP15-Inh	*Padmanabhan et al. (2018);* *Fukushima et al. (2017);* *Ward et al. (2018);* *Niederkorn et al. (2022)*
USP16	high expression	stabilization of c-Myc protein levels	c-Myc	unknow	*Ge et al. (2021)*
USP17	high expression	regulation of EMT signaling pathway inhibition of USP17 can promote ROS production and inhibit NF-kB and p56	EMT	unknow	*Baohai et al. (2019)*
USP19	unknow	regulation of p27^{Kip1} level	unknow	unknow	*Lu et al. (2011)*
USP22	high expression	regulation of AR and c-Myc dual signaling pathway	AR AR-v7 c-Myc	unknow	*Schrecengost et al. (2014);* *McCann et al. (2020)*
USP25	low expression (mRNA)	regulation of Wnt signaling pathway	TNKS	unknow	*Chen et al. (2021b);* *Cheng et al. (2019a)*
USP26	low Expression	regulation of AR signaling pathway	AR	unknow	*Wosnitzer et al. (2014);* *Dirac & Bernards (2010)*
USP33	high expression	regulation of DUSP1-JNK singaling axis stabilization of c-Myc protein levels	DUSP1 c-Myc	unknow	*Guo et al. (2020);* *Ding et al. (2021)*
USP39	high expression	regulation of EGFR signaling pathway	EGFR	unknow	*Huang et al. (2016);* *Thoma (2017)*
USP44	high expression	stabilization of EZH2 protein levels	EZH2	unknow	*Park et al. (2019)*
USP46	unknow	regulation of AR-AKT-MDM2-p53 signaling pathway stabilization of AR, MDM2 and PHLPPs protein levels	H2A H2B AR MDM2	unknow	*Li et al. (2013);* *McClurg et al. (2018a)*

PHLPPs

4 **Note:**

5 USPs, ubiquitin-specific peptidases; KDM4A, histone demethylase lysine-specific demethylase 4A; GRP75,

6 glucose regulated protein 75; SIX1, sine oculis homeobox homolog 1; MDM2, murine double minute 2; FAS,

7 fatty acid synthase; ACDase, acid ceramidase; KDM6A, histone demethylase lysine-specific demethylase

8 6A/UTX; MDMX, murine double minute X; AR, androgen receptor; ERG, ETS-related gene; MMP9, matrix

9 metalloproteinase 9; DRP1, dynamin-related protein 1; PBX1, Pre-B cell leukemia homeobox-1; G3BP2,

10 GTPase-activating protein-binding protein 2; ATF2, transcription factor 2; IGF, insulin growth factor; EMT,

11 epithelial-mesenchymal transition; DUSP1,dual-specificity phosphatase-1; JNK, cJUN NH2-terminal kinase;

12 EGFR, epidermal growth factor receptor; EZH2, enhancer of zeste homolog 2.