Prion protein and cancers

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The normal cellular prion protein, \( \text{PrP}^\text{C} \), is a highly conserved and widely expressed cell surface glycoprotein in all mammals. The expression of \( \text{PrP} \) is pivotal in the pathogenesis of prion diseases; however, the normal physiological functions of \( \text{PrP}^\text{C} \) remain incompletely understood. Based on the studies in cell models, a plethora of functions have been attributed to \( \text{PrP}^\text{C} \). In this paper, we reviewed the potential roles that \( \text{PrP}^\text{C} \) plays in cell physiology and focused on its contribution to tumorigenesis.

**Keywords** prion protein; prion disease; tumorigenesis

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Introduction

Transmissible spongiform encephalopathies, aka, or prion diseases are a group of fatal neurodegenerative disorders that affect animals and humans. However, human prion diseases are rare and the incidence is \( \sim 1.5 \) cases per million people per year [1].

Prion diseases can be infectious, genetic, and sporadic in nature. The word prion was coined by Stanley Prusiner as an abbreviation for ‘proteinaceous infectious particle’ [2], which described the infectious entity of a protein responsible for the pathogenesis and transmission of the diseases. The concept of prion is consistent with an earlier ‘self-replicating’ hypothesis postulated by Griffith, in attempts to explain the infectious agent that causes scrapie [3]. It is believed that a conformationally altered isoform of a normal cellular prion protein (\( \text{PrP}^\text{C} \)), called scrapie \( \text{PrP} \) (\( \text{PrP}^\text{Sc} \)) is the sole etiologic agent of prion diseases. \( \text{PrP}^\text{Sc} \), a \( \beta \)-sheet-rich conformer upon interacting with \( \text{PrP}^\text{C} \) can convert the \( \alpha \)-helices-rich \( \text{PrP}^\text{C} \) into \( \text{PrP}^\text{Sc} \). The exact process by which this conversion occurs remains incompletely understood. How \( \text{PrP}^\text{Sc} \) causes neuronal cell death is also poorly understood.

The physiological functions of \( \text{PrP}^\text{C} \) remain enigmatic because \( \text{PrP}^\text{C}^-^-^-^- \) (knockout) mice/cattle do not show any obvious phenotype [4–9]. Furthermore, Norwegian dairy goats, lacking prion protein naturally due to a non-sense mutation in the \( \text{PRNP} \) are also healthy [10]. But some reports suggested that \( \text{PRNP}^-^-^-^- \) mice had minor aberrant phenotypes [11–14]. Contrast to in vivo studies, in cell models, \( \text{PrP}^\text{C} \) has been reported to have a plethora of functions embracing all aspects of cell biology. The functions that have been attributed to \( \text{PrP}^\text{C} \) include anti-apoptosis, pro-apoptosis, metal homeostasis, anti-oxidative damage, cell adhesion and migration, signaling, immune modulation, and cell differentiation, etc. [15–22]. Many of these functions are incongruous with the fact that animals lacking \( \text{PrP}^\text{C} \) either by genetic engineering or due to natural mutation appear to be normal.

The prion gene family is composed of four members: \( \text{PRNP} \), \( \text{PRND} \), \( \text{PRNT} \), and \( \text{SPRN} \) (Fig. 1). \( \text{PRNT} \) is a pseudogene (Fig. 1). In humans, \( \text{PRNP} \), \( \text{PRND} \), and \( \text{PRNT} \) are located at p12/p13 on chromosome 20, and the \( \text{SPRN} \) is localized on chromosome 10. \( \text{PrP}^\text{C} \) is a glycosylphosphatidylinositol (GPI)-anchored cell surface glycoprotein containing 231 amino acids. It is highly conserved among all vertebrates, though the sequence identity is low between the mammals and non-mammals. The \( \text{PrP}^\text{C} \) is first synthesized as a pre-pro-\( \text{PrP} \) with a leader peptide (1–22) at the N-terminal, and a GPI anchor signaling peptide (GPI-PSS) at the C-terminal (232–253). The leader peptide guides the pre-pro-\( \text{PrP} \) into the endoplasmic reticulum (ER) where it is cleaved to generate pro-\( \text{PrP} \). Like other GPI-anchored proteins, pro-\( \text{PrP} \) is then translocated from the ER to the Golgi with the help of Post-GPI Attachment To Proteins 1 and 5 (PGAP1 and PGAP5) [23,24]. Association of \( \text{PrP}^\text{C} \) with lipid rafts in ER may be important for its correct folding and glycosylation and...
thus transportation to the Golgi [25,26]. In the Golgi, pro-PrP is further processed with the addition of N-linked glycans, removal of the GPI-PSS, and addition of the pre-assembled GPI anchor [25,26]. Finally, the mature PrP\(^C\) is translocated to the outer leaflet of the plasma membrane. The GPI anchor modification is a complex phenomenon involving in at least 24 gene products [27,28]. It is not known why the GPI-PSS of PrP is more homologous comparing with the N-terminal peptide sequence among PrP sequences from different species.

Besides residing on the cell membrane, PrP\(^C\) has also been detected in the cytosol of some neurons in the hippocampus, neocortex, thalamus, and some cancer cells [29,30]. In addition, PrP is detected in the nucleus of colorectal and breast cancer cells [31,32]. However, it is not clear whether these unconventional PrPs are mature PrP\(^C\), pro-PrP, or pre-pro-PrP [33].

**PrP and Prion Diseases**

The majority of prion disease (>85%) is sporadic without known genetic or infectious sources. Infectious prion diseases accounts for <2% of all cases, and the dominant inherited prion disease accounts for about 15% of all prion diseases and is linked to germline mutations in PRNP [34].

More than 30 mutations have been identified spanning the whole sequence, including mutations inside the GPI-PSS [35]. Based on earlier in situ hybridization studies, the expression of PRNP mRNA was found to be developmentally regulated, and was implicated to be important in the embryogenesis and development [36,37]. This interpretation was abandoned when it was found that two PRNP\(^{-/-}\) mouse lines, Zurich I and Npu, did not show obvious phenotype [38,39]. The next three PRNP-ablated mouse lines, Ngsk, Rcm0, and Zurich II did show severe ataxia and Purkinje cell degeneration at later ages [40–42]. However, it was later demonstrated that such phenotype is the result of the over-expression of PRND, not the ablation of PRNP [41–43].

In addition to PRND, transgenic mice over-expressing PRNP\(_b\) (an allele with 108Phe and 189Val) other than PRNP\(_a\) (an allele with 108Leu and 189Thr) develop ataxia, hind limb paralysis, and tremors [44,45]. Moreover, deletion of PRNP\(_a\) allele from 32–121 or 32–134 and re-introduction of the allele into Zurich I mice resulted in neurodegeneration of granule cell layer in relatively young mice [46]. Neurodegeneration has also been observed in transgenic mice expressing extra octapeptide repeats [47,48]. Although the aforementioned transgenic mice expressing truncated PrP develop neurodegeneration similar to prion diseases, it is still unknown why deletion of 114–121 in PrP\(^C\) does not lead to neurodegeneration [49] (Fig. 2).

Depletion of Shadoo was previously implicated as a potential mechanism accounting for prion diseases [50]. Subsequent results revealed that reduction of Shadoo in PrP\(^{Sc}\) infected mice was PrP\(^{Sc}\) strain specific [51] and the over-expression or reduction of Shadoo did not affect the PrP\(^{Sc}\) pathogenesis [52,53].

**PrP\(^C\) in Cell Adhesion and Migration**

Many studies have been reported that PrP\(^C\) can stimulate the outgrowth of neurite [54–59]. Binding between PrP\(^C\) and sulfated glycosaminoglycans [60], the components of extracellular matrix proteins, suggested that PrP\(^C\) may participate in cell adhesion. PrP\(^C\) also binds other extracellular matrix or cell surface molecules, such as neural cell adhesion molecule (NCAM), selectins, laminin, laminin receptor, and stress-inducible protein-1 [61–65]. Thus, it is highly likely that PrP\(^C\) participate in cell adhesion. Compared with control cells, N2a cells treated with phosphatidylinositol-specific phospholipase C (PI-PLC) to remove the cell surface GPI-anchored protein aggregated to a much reduced extent. This aggregation is also greatly reduced in the presence of an anti-N-terminus-specific

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*Figure 1. Secondary structure of the prion protein family*
anti-PrP monoclonal antibody [66]. In PC12 cells, neuronal growth factor induces the expression of PrP(C) and specific anti-sera to PrP(C) block 50%–70% of the neuritogenesis, implicating that PrP(C) is critical for PC-12 cell adhesion and neurite outgrowth [62]. It is possible that a cell surface protein such as NCAM, laminin, or vitronectin can interact with cis-/trans-acting PrP(C) to induce neurite outgrowth. Both cis and trans interactions between NCAM on the neuronal surface and PrP promote recruitment of NCAM to lipid rafts and regulate the activation of Fyn kinase, an enzyme involved in NCAM-mediated signaling [54]. When these interactions are disrupted in NCAM-deficient and PrP-null neurons or by PrP antibodies, NCAM/PrP-dependent neurite outgrowth is arrested, because the cis and trans interactions between PrP(C) and NCAM play a critical role for neurite outgrowth [54]. In addition, PrP(C), by interacting with contactin-associated protein (Casp), regulates the proteolysis of Casp on the cerebellar neuronal cell surface and inhibits neurite outgrowth [67]. Thus, whether or not PrP(C) stimulates neural cell growth depends on its interacting partner.

In mouse brain endothelial cells, PrP(C) co-localized with the adhesion molecule platelet endothelial cell adhesion molecule-1 in raft membrane microdomains. Anti-PrP(C) antibodies inhibit transmigration of U937 human monocytic cells as well as freshly isolated monocytes through human brain endothelial cells, thus supporting the notion that PrP(C) is expressed by brain endothelium as a junctional protein that is involved in the trans-endothelial migration of monocytes [68]. In N2a or HeLa cells, PrP(C) accumulates at focal adhesions (FAs). However, the down-regulation of PrP(C) leads to reduced FA numbers, and increased FA length, along with Src and focal adhesion kinase (FAK) activation whereas PrP(C) over-expression elicits the formation of novel FA-like structures [69]. In a zebrafish model, loss of PrP(C) results in the loss of embryonic cell adhesion and arrests gastrulation, and PrP mediates Ca2⁺-independent homophilic cell adhesion and signaling as well as modulating Ca2⁺-dependent cell adhesion by regulating the delivery of E-cadherin to the plasma membrane [70].

Compared with wild-type (WT) mice, the intestines from PRNP−/− mice had greater paracellular permeability and impaired intercellular junctions, but did not develop spontaneous disease [6]. It was shown that in cell contact areas of PrP(C) down-regulated cells, the levels of E-cadherin, desmoplakin, plakoglobin, claudin-4, occludin, zonula occludens 1, and tricellulin were reduced.

**PrP(C) in Cell Proliferation, Cell Differentiation, and Cell Death**

PrP(C) has been reported to play a role in T lymphocyte proliferation [71]. The T-cell mitogen concanavalin A-induced proliferation of lymphocytes from PrP−/− mice was significantly reduced to ~50%–80% of that of WT (PrP+/+) mice.
48 h post-stimulation [72]. However, others were unable to confirm these results [73].

In vivo, in the subventricular zone, mice that over-express PrP^C have more proliferating cells compared with the WT or PrP^C/−/ mice; in the dentate gyrus (DG), PrP^C over-expression and WT mice have more proliferating cells compared with the PrP^C/−/ mice. However, the final number of neurons produced in the DG is unchanged by PrP^C expression, thus other factors must control the ultimate fate of new neurons [74]. On the contrary, the oligodendrocyte precursor cells that lack PrP^C proliferate more vigorously at the expense of a delay in differentiation [75]. Thus, it appears that the effects of PrP^C on cell proliferation are cell-context dependent.

Another important aspect PrP^C involved in is cell death or apoptosis. Cell lines derived from WT or PrP null mice hippocampal neurons showed different response to serum deprivation. PrP ablated cells died quickly whereas WT counterpart cells could survive serum deprivation [20]. It is reported that H_2O_2-treated PRNP^+/−/ cells were impaired in autophagic flux, whereas H_2O_2-treated WT cells showed enhanced autophagic flux [76]. However, in T98G human glioma cells, silencing PrP resulted in autophagy-dependent cell death as evidenced by the up-regulation of LC3-II, Beclin-1 and a concomitant decrease of p62, Bcl-2, and phosphorylated 4E-BP1 [77]. PrP^C delays Bax conformational change required for the induction of mitochondrial release of cytochrome C in human and mouse neuronal cells and MCF7 breast cancer cells [78]. The expression of PrP^C reduces ischemic insult to the mouse brain [79]. However, it is unknown why only male hippocampal neurons are more susceptible to ischemic insult in Ngsk PRNP^+/−/ mice [80]. Contrary to neuroprotection, the over-expression of WT PrP^C resulted in degeneration of the central nervous system, in addition to peripheral neuron and skeletal muscle loss [44]. It has been shown that the over-expression of PrP^C may trigger p53-dependent caspase-3 activation and result in cell apoptosis [15]. It is possible that the different roles played by PrP^C in neuron may depend on whether the cells are under oxidative stress or ER stress [81]. However, in breast cancer cells, ER stress induces PrP^C expression which is associated with cytoprotection [31].

**PrP^C in Cancers**

Resistance to apoptosis is one of the most important features for cancer cells contributing to tumorigenesis as well as drug resistance. Cell death resistance can be the results of aberrant expression of proteins having anti-apoptotic function or down-regulation of pro-apoptotic proteins, which can be the outcome of either epigenetic modification or oncogene over-expression. Although the exact function of PrP^C is unknown, several lines of evidence suggested that PrP^C is involved in cell adhesion, migration, proliferation, differentiation, ion homeostasis, and signal transduction (see above). All these functions implicated that PrP may be involved in tumorigenesis. In fact, the up-regulation of proteins of PRNP family has been detected in many different tumor tissues and cancer cell lines including breast cancer, colorectal cancer, gastric cancer, prostate cancer, melanoma, pancreatic ductal adenocarcinoma, glioma, and osteosarcoma [77,78,82–88].

**Breast cancer**

The expression and functions of PrP in breast cancers have been extensively studied during the last decade [78,84,89,90]. Higher PrP mRNA levels in breast tumor were due to ER stress and are associated with a poor prognosis [31]. When comparing the gene expression of TNF sensitive and resistant MCF-7 cells, Roucou et al. [78] found that PrP was up-regulated more than 3 folds determined by microarray and 17 folds determined by quantitative polymerase chain reaction. When treated with TNF, the resistant cells did not undergo cytochrome C release and nuclear condensation. In PrP expressing MCF-7 cells, the translocation of EGFP-Bax to mitochondria is partially inhibited and Bax-mediated cytochrome C release is prevented. It is likely that PrP inhibits the very first step of Bax pro-apoptotic activation and does not function exactly like Bcl-2.

Besides TNF, PrP is also involved in the resistance of breast cancer cells to adriamycin (ADR) and TRAIL-mediated cell death. It was shown that ADR and TRAIL resistant cells still express TRAIL receptors (TRAIL-Rs), actually in the case of TRAIL-R2, the expression level is much higher. These data suggested that cellular factor(s) other than TRAIL-Rs results in the resistance. One of the cellular factors associated with ADR and TRAIL-mediated cell death is PrP. Knockdown of PrP does not affect the formation of TRAIL DISC, but down-regulates the expression of Bcl-2 and facilitates the cleavage of Bid, thus resulting in cell death [90]. In addition, PrP was found to co-express and co-localize with P-glycoprotein (P-gp) in ADR-resistant breast cancer cells MCF7/ADR. When PrP was knocked down, paclitaxel, a P-gp substrate, showed reduced capability to induce *in vitro* invasion of the cells [91]. More importantly, tissue microarray analysis from 756 breast cancer tumors showed that PrP is associated with ER-negative (ER^−) breast cancer subsets, and compared with ER^+/−/PrP^++/ patients, ER^−/−/PrP^−−/ patients are more susceptible to adjuvant chemotherapy [84]. On the contrary, Yu et al. [92] found that although the PrP knockdown breast cancer cells MDA-MB-435 are more susceptible to serum deprivation, they are more resistant to doxorubicin, a DNA-interacting chemotherapy drug. The resistance is independent of p53 but involved in extracellular signal-regulated kinases (ERK) pathway. These data suggested that the expression of PrP that confers certain drug resistance may be cell- or drug-specific, which supported the notion that PrP might be useful for molecular typing for personalized treatment.
Colorectal cancer

Studies on Caco-2/TC7 cells showed that PrP interacts with desmosomal proteins, including Desmoglein 2, Plakophilin 2a, plakoglobin, α2 spectrin, etc., in rafts, and can be localized into the nuclei [32]. This abnormal distribution suggested that PrP might contribute to colon cancer cell tumorigenesis. After PrP was knocked down in DLD-1 and SW480 colon cancer cells, the proliferation of cancer cells was significantly reduced. It has been shown that after PrP was silenced, the expression of GLUT1 was significantly alleviated by reducing the binding between HIF-2α and the promoter region of GLUT1 [93]. It is possible that PrP localized in the nuclei can facilitate the binding between HIF-2α and the promoter. Interestingly, knocking down PrP expression further reduces the glycolysis in DLD-1 and SW480 cells. PrP was also identified as a biomarker for colon cancer during adenoma to carcinoma transition [94]. Microarray analysis of relapsed and non-relapsed patients revealed that PRNP is over-expressed in relapsed patients (median expression level of 0.1874 in carcinoma compared with median expression level of 0.1266 in normal tissue). More importantly, primary site and up-regulation or down-regulation of PRNP was proved to have prognostic value with regard to the 3-year survival of the patients [85]. Thus, PrP might be a valid target for colon cancer diagnostics and treatment. In fact, treatment of HCT116 cancer cells with anti-PrP specific antibodies (BAR221 and F89/160.15) effectively reduced the growth of cancer cells and enhanced the effect of irinotecan, 5-FU, cisplatin, and doxorubicin to varying degrees [95].

Gastric cancer

PrP is expressed in the mucosa of the gastrointestinal tract in different mammal species. Its expression is up-regulated in the mucosa of patients with Helicobacter pylori gastritis [96], which might be the result of H. pylori-induced hypergastrinemia and increased mucosal PGE(2) and IL-1β synthesis [97]. Since H. pylori can induce gastric cancer, it is reasonable to assume that PrP may contribute to gastric tumorigenesis. To investigate the role PrP plays in gastric cancer, immunohistochemical staining of normal gastric mucosa, well-differentiated, and poorly differentiated gastric carcinoma showed that PrP is over-expressed in poorly differentiated cancer tissues. A modified subtractive hybridization method identified PRNP being one of the up-regulated genes from vincristine (VCR)- and ADR-resistant gastric adenocarcinoma cell lines derived from SGC 7901 [98]. Immunoblotting proves that PrP in VCR- and ADR-resistant cell lines is up-regulated and is PK-sensitive, suggesting that the PrP is a PrP⁵. Besides resistant to ADR and VCR treatment, higher PrP expressing cells are also more resistant than PrP down-regulated cells when treated with VP-16, 5-FU, and CDDP. However, PrP seems not to affect cell sensitivity to CTX, Ara, and MTX treatment [83]. For resistance to ADR and VCR, it is shown that PrP expression up-regulated the expression of P-gp through multiple drug resistant (MDR)-1 [99]. Since ADR, VCR, and VP-16 are P-gp related drugs whereas 5-FU, CDDP, CTX, Ara, and MTX are P-gp non-related drugs, the resistance of PrP expression cells to 5-FU and CDDP suggested that PrP might be a better biomarker for gastric cancer cells drug resistance. It will be important to understand why cells expressing PrP have wider range of drug resistance than P-gp expressing cells.

Besides drug resistance, PrP also plays a role in gastric cancer tumorigenesis. PrP down-regulated cancer cells have significantly reduced capability to invade in matrigel assay. It is probable that the p-ERK-MMP11 pathway is involved [100]. Accordingly, cancer cells expressing higher level of PrP are more likely to migrate than lower PrP expressing cancer cells in vivo. The expression of PrP in gastric cancer cells also enhanced cell proliferation, anchorage independent growth, and accordingly increased tumor growth after being xenografted into nude mice [101]. It has been shown that PrP promotes G0/G1 to S-phase transition by up-regulation of cyclin D1 and possibly CDK4. The effect of PrP⁵ on phosphorylated Akt (p-Akt) and total Akt seems inconsistent as the over-expression of PrP causes up-regulation of p-Akt but not total Akt, whereas knocking down PrP results in down-regulation of p-Akt and total Akt [99]. However, PrP might activate the transcription of P-gp or even interact with P-gp to affect cancer cells MDR [91,99]. It is likely that the amino acids from 24 to 50 of PrP are responsible for the proliferation of PrP expression cells, because when this domain is deleted, the cells proliferation capability is significantly reduced. On the contrary, deletion of octapeptide repeats (amino acids 51–91) does not affect gastric cancer cell adhesion, invasion, apoptosis, and MDR [102]. However, why N-terminal deletion reduces cell proliferation is not clear. To answer this, it would be important to detect the change of expression level of p-Akt in N-terminus deleted PrP transfected cells, if p-Akt pathway is really involved in cell proliferation. Overall, PrP might be a potential biomarker for gastric cancer chemoresistance and poor prognostics [103].

Pancreatic ductal adenocarcinoma

The mRNA of PrP was first demonstrated to be up-regulated in pancreatic ductal adenocarcinoma (PDAC) cell lines [104]. It was also found that high levels of PrP protein were detected in a panel of seven PDAC cell lines. Distinct from PrP from the other cancer cells, PrP expressed in PDAC is pro-PrP, as defined by retaining its GPI-peptide signal sequence. This conclusion is supported by the following lines of evidence: (i) PrP is resistant to PI-PLC, an enzyme that cleaves the GPI anchor; (ii) PrP is sensitive to carboxypeptidase, indicating that the C-terminal of the PrP is not protected by a GPI anchor; (iii) PrP is no longer in lipid raft; (iv) cell surface PrP has a much longer half-life than
GPI-anchored PrP; and (v) an anti-serum specific for the GPI-PSS of PrP reacts with PrP, but not with the mature PrP. Since the GPI-PSS is highly homologous to a traditional transmembrane domain, in PDAC cell lines, the pro-PrP is present on the cell surface using the GPI-PSS as a putative transmembrane domain.

Most importantly, it was found that while PrP was undetectable by immunohistochemical staining in normal pancreatic ductal cells, it was highly expressed in about 50% of the PDAC biopsies [86]. Furthermore, the expression of PrP is a marker of poor prognosis in four different cohorts of PDAC patients [105]. Our finding that PrP is undetectable in normal human pancreatic ductal cells is further supported by our recent results that PrP is also undetectable in a normal human pancreatic ductal epithelial cell line CRL-4023 under our study conditions (data not shown).

The underlying mechanism triggering the accumulation of pro-PrP in PDAC is not known. The ER quality control system detects the improperly processed or misfolded protein and guides its degradation by the proteasome [106]. A defect in the proteasome or the ER quality control mechanism may thus cause the accumulation of the pro-PrP. In addition, a defect in the GPI anchor modification pathway may also contribute to the accumulation of pro-PrP. It is interesting to note that others have reported that the GPI-PSS of PrP is by far the most inefficient GPI-PSS in an in vitro GPI modification assay [107]. Therefore, a slight defect in the GPI-anchor modification pathway will have a much more dramatic effect on the PrP than other GPI-anchored proteins.

To directly address the latter possibility, we sequenced the 24 genes that have been reported to be required for the synthesis of the GPI anchor in one of the PDAC cell line, BxPC3. We compared the sequences in BxPC3 cells to the published sequences of the 24 genes. Six sense and eight synonymous mutations in five genes were identified (data not shown). We also compared the expression levels of the 24 genes with those from a neuroblastoma cell line, in which PrP exists as a GPI-anchored PrP, and thus presumably should have all the 24 genes functioning properly. It was found that the expression levels of most of the genes were significantly reduced (data not shown).

Unexpectedly, a binding motif for filamin A (FLNa) exists in the GPI-PSS of PrP. In vitro pull-down experiments demonstrated that pro-PrP binds to at least two domains of FLNa [108] and the binding between pro-PrP and FLNa requires the last five amino acids of the GPI-PSS. It is important to note that a peptide corresponding to a portion of the PrP GPI-PSS can compete with pro-PrP in binding to FLNa. Binding of pro-PrP to FLNa alters the FLNa distribution and phosphorylation of downstream signaling molecules such as LIMK1, LIMK2, and coflin that are important in the organization of the actin filaments. When PrP is knocked down, the total amount of FLNa is not changed, but it seems that FLNa retreats from the cell surface based on immunofluorescent staining and the distribution of phosphorylated proteins changed significantly. In addition, PDAC cells expressing PrP proliferate and migrate faster. It is easy to understand why pro-PrP/FLNa interaction increases cell migration. Whether or not increased cell proliferation is directly

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Figure 3. Over-expression of PrP in prostate cancer, hepatocellular carcinoma (HCC), and OSCC. Prostate cancer, HCC, and OSCC express higher level of PrP compared with prostate benign lesion, normal liver tissue, and oral leukoplakia.
due to such an interaction is unknown. It has been reported that cytoskeleton change through activated FAK at tyrosine 397 and 925 of fibroblast 3Y1 cells stimulates mitogen-activated protein kinases pathway and finally results in cell proliferation [109]. Another potential pathway involved in cytoskeleton change and proliferation is Rho-GTPases-PI3K-Akt [110]. It will be important to dissect the contributions of pro-PrP/FLNa interaction in modulating these pathways.

**Melanoma**

PrpC is undetectable in normal human skin. However, it has been reported that in inflamed skin tissues, some infiltrating monocytes and keratinocytes do express PrP [111]. It was found that while normal melanocytes did not express PrP, high level of PrP was detected in invasive melanoma [108]. The Prp expressed in a melanoma cell line, M2, is also pro-PrP. In A7 cells, pro-PrP co-localizes and co-purifies with FLNa. Knocking down Prp in A7 cells greatly reduces their migration in a wound healing assay. Therefore, the presence of pro-PrP is not only limited to PDAC.

**Other tumors**

Earlier, Sauer *et al.* [82] suggested that the over-expression of PrP in prostate spheroids is a response to reactive oxygen species and inversely correlated with the diameter of the spheroids. More recently, we also detected the over-expression of PrP in about 90% prostate tumor biopsies. However, whether the expression of PrP has any diagnostic or prognostic value is not known. Similarly, we also detected the over-expression of PrP in hepatocellular carcinoma and in oral squamous cell carcinoma (OSCC) (Fig. 3). Therefore, it appears that PrP up-regulation is a common phenomenon in many types of cancers but only in some portion of patients for a specific cancer type, which may be associated with tumor progression or drug resistance. Thus, understanding the function of PrP in tumorigenesis will help to develop another therapeutic target for personalized cancer treatment. Besides *PRNP, PRND* is also up-regulated in osteosarcoma [88,102]. However, the exact function of the up-regulated *PRNP* or *PRND* still needs further exploration.

**Conclusion**

A plethora of capricious functions have been attributed to PrpC, but many of these studies showed conflicting results. Many of these conclusions are also inconsistent with reality, because the expression of PrpC is not essential for life. It is clear that PrpC does participate in some biological pathways, but whether or not some of the reported results are really due to PrpC is worth of serious re-evaluation.

Many reports have shown that PrP is up-regulated in cancer cell lines and tumor tissues. The underlying mechanism that induced or up-regulated the expression of PrP is most likely tumor type dependent. While a few studies of PrP have reported that the expression of PrP is a marker of poor prognosis, whether PrP has any clinical applications will depend on additional studies with much larger sample size and in different cohorts of patients.

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**References**


