The Role of Cellular Prion Protein in Cancer Biology: A Potential Therapeutic Target

Manqiu Ding¹, Yongqiang Chen², Yue Lang¹ and Li Cui*¹

¹ Department of Neurology, The First Hospital of Jilin University, Changchun, China, ² CancerCare Manitoba Research Institute, CancerCare Manitoba, University of Manitoba, Winnipeg, MB, Canada

Prion protein has two isoforms including cellular prion protein (PrPC) and scrapie prion protein (PrPSc). PrPSc is the pathological aggregated form of prion protein and it plays an important role in neurodegenerative diseases. PrPC is a glycosylphosphatidylinositol (GPI)-anchored protein that can attach to a membrane. Its expression begins at embryogenesis and reaches the highest level in adulthood. PrPC is expressed in the neurons of the nervous system as well as other peripheral organs. Studies in recent years have disclosed the involvement of PrPC in various aspects of cancer biology. In this review, we provide an overview of the current understanding of the roles of PrPC in proliferation, cell survival, invasion/metastasis, and stem cells of cancer cells, as well as its role as a potential therapeutic target.

Keywords: cellular prion protein, cancer, proliferation, metastasis, drug resistance, cancer stem cell

INTRODUCTION

Prion protein (PrP) is expressed throughout the whole body. It has two isoforms, cellular prion protein (PrPc) and its pathogenic form-scrapie prion protein (PrPSc) (1, 2). PrPSc is well known for its ability to cause a series of neurodegenerative diseases in human and other mammals (1, 3). It results from post-translational conversion of the glycosylphosphatidylinositol (GPI)-anchored PrPC (4, 5). PrPC, as a scaffold on the cell surface, recruits different partners to execute its functions being involved in signaling pathways (6). The biosynthetic pathway of PrPC is similar to that of other membrane-attached and secreted proteins (5) (Figure 1). It is synthesized in endoplasmic reticulum (ER)-attached ribosomes followed by its import into ER where it is glycosylated and modified by GPI anchor before it is transported into Golgi for further modification. Then PrPC is transported to the cell surface where it can be internalized through endocytic pathway (7). The internalized PrPC can be transported into the lysosome for degradation or be enclosed in exosomes and secreted.
outside the cells (7). PrPC is mainly attached to lipid rafts on the cell surface via its C-terminal GPI anchor (8, 9). It is also located in the cytosol and the nucleus (10–12). Interestingly, PrPC was found in the exosomes secreted by cancer cells (13).

Cancer is the second leading cause of death worldwide. Studies in recent years show that PrPC is involved in various aspects of cancer biology such as cell proliferation, metastasis, cell death, drug resistance and cancer stem cells (14–21). In this review, we summarize the current progress in these aspects.

**PrPC PROMOTES CANCER CELL PROLIFERATION**

PrPC can promote proliferation in cancer cells (22). Liang et al. demonstrated that overexpression of PrPC promoted cell proliferation through activation of the phosphatidylinositide 3-kinase (PI3K) pathway and promotion of the G1/S phase transition by upregulating cyclin D1, in gastric cancer cells (22). PrPC is also involved in G1 to S phase transition in renal adenocarcinoma ACHN and colon adenocarcinoma LS 174T cells (23). Knockdown of PrPC inhibited cell proliferation and amplified the inhibitory effect of fucoidan on cell proliferation by suppressing expression of cyclins and cyclin-dependent kinase (CDK), in HT29 colon cancer cells (24). Interaction of PrPC with the co-chaperone Hsp70/90 organizing protein (HOP) promoted proliferation via activating PI3K and extracellular-signal-regulated kinase (ERK1/2) pathways in glioblastomas (GBM) cells (25). Furthermore, HOP-PrPC interaction promoted proliferation of glioblastoma stem-like cells and the decrease expression of PrPC and HOP may work as an effective therapy for GBM in the future (26). Warburg effect refers to the event that cancer cells preferentially use aerobic glycolysis to generate energy and reducing power for their biosynthesis, cell survival and proliferation (27). Overexpression of PrPC mediated Warburg effect by increasing glucose transporter 1 (Glut1) expression which promotes glucose uptake through epigenetic activation of Fyn-HIF-2α-Glut1 pathway in colorectal cancer cells (28). PrPC can also increase cell proliferation by interacting with 37/67 kDa non-integrin laminin receptor (LR/37/67 kDa) and activating downstream ERK1/2 and PI3K/protein kinase B (AKT) signaling pathways in schwannoma cells (29). It promoted proliferation by interacting with Notch1 in pancreatic ductal adenocarcinoma (PDAC) (30). A variant of PrPC with one octapeptide repeat deletion (1-OPRD) is widely present in gastric cancer cell lines and gastric cancer tissues (31).
Overexpression of 1-OPRD could promote the proliferation of gastric cancer cells through transcriptional activation of cyclin D3, which facilitated the G1/S-phase transition in cell cycle (32).

**PrP C PROMOTES CANCER CELL INVASION/METASTASIS**

Metastasis leads to more than 90% of cancer-caused death, but its underlying mechanisms still remain poorly understood (33). Christine L et al. divided the process of metastasis into two phases: the first phase is physical translocation of cancer cell from a primary tumor to other distant tissues, and the second phase is colonization of metastatic cancer cells in their new microenvironment (33). EMT refers to epithelial-to-mesenchymal transition (34). Many in vitro models show that EMT act as a key process during cancer metastasis (35, 36). Transcription of Prnp (the gene encoding PrP) considerably increased during EMT (37). Upregulation of PrPC and dedifferentiation of EMT-like cells were observed in invasive colorectal cancer cells (CRC) (18, 38). Overexpression of PrPC by transfecting pCDNA3.0-Prnp in SW480 cells led to EMT whereas, knockdown of Prnp in mesenchymal-like LIM2405 cells caused MET (mesenchymal-to-epithelial transition) (18). The mechanisms underlying EMT enhancement by PrPC are largely unclear.

SATB1 (special AT-rich sequence-binding proteins 1) is a nuclear matrix associated protein. It can induce tumor metastasis by altering chromatin structure and upregulating metastasis-associated genes while downregulating tumour-suppressor genes (39, 40). Knockdown of Prnp resulted in loss of SATB1 expression and reduction of metastatic capacity in CRC with Fyn and specificity protein 1(SP1) being involved in this process, indicating that PrPC may promote tumor metastasis via upregulating the PrPC-Fyn-SP1-SATB1 axis (18). PrPC and γ-Syn are overexpressed in CRC (41, 42). They may be involved in colorectal cancer cell metastasis by inducing an endothelial proliferation to differentiation switch (42, 43).

PrPC is highly expressed in metastatic gastric cancer cells and it may promote invasion and metastasis through activation of the mitogen-activated protein kinases (MEK)/ERK pathway and consequent transactivation of matrix metalloproteinase-11 (MMP11) (44). MMP11 can promote matrix degradation, inflammation and tissue remodeling (20, 44). Its N-terminal fragment is essential for transducing invasion-promoting signal of PrPC (20, 44). Tissue Inhibitor of Metalloproteinase (TIMP) is fragment is essential for transducing invasion-promoting signal.

**PrP C PROMOTES CANCER CELL DRUG RESISTANCE**

One major challenge for cancer treatment is drug resistance. Various mechanisms can contribute to cancer drug resistance (54). The most studied mechanisms involving the roles of PrPC in cancer drug resistance include multi-drug resistance (MDR) and inhibition of cell death. Multi-drug resistance (MDR) refers to the ability of cancer cells to survive against a wide range of anti-cancer drugs (55). Cell death can be classified into three main types including apoptosis (Type I programmed cell death), autophagic cell death (Type II programmed cell death) and necrosis (56). Apoptosis is characterized by cell shrinkage, membrane blebbing, chromatin condensation, DNA fragmentation and caspase activation. Autophagic cell death is induced by the over-activation of autophagy that is an intracellular lysosomal degradation process. Necrosis is a non-programmed cell death. It is caused by sudden results to the cells and is characterized by breakage of plasma membrane followed by cytoplasmic leakage.

Upregulation of PrPC can lead to drug resistance in different types of cancers cells (57–59). In colorectal cancer...
cells, PrP<sup>C</sup> is involved in 5-FU resistance by increasing cell survival and proliferation via activating PI3K-Akt signaling pathway and the expression of cell cycle-associated proteins (59). PrP<sup>C</sup> overexpression led to resistance of colorectal cancer LS174T cells to doxorubicin-induced apoptosis by upregulation of the inhibitors of apoptosis proteins (IAPs) (60). Upregulation of PrP<sup>C</sup> leads to increased superoxide dismutase and catalase activities and decreased endoplasmic reticulum stress and apoptosis, which results in oxaliplatin resistance in colorectal cancer cells (61, 62). In gastric cancer cells, PrP<sup>C</sup> can promote drug resistance by different mechanisms. PrP<sup>C</sup> coexists with MGr1-Antigen/37 kDa laminin receptor precursor (MGr1-Ag/37LRP) to promote MDR in gastric cancer cells by inhibiting apoptosis via activation of the PI3K/AKT signaling pathway (63). Octarepeat peptides of PrP may be involved in gastric cancer MDR by increasing the activities of antioxidant enzymes (64). PrP<sup>C</sup> can promote MDR by upregulating the multidrug resistance protein (P-gp) and suppressing apoptosis in gastric and breast cancer cells (65, 66). Overexpression of PrP<sup>C</sup> promotes resistance to TNF-α-induced apoptosis by inhibiting Bcl-2-associated X protein (Bax) expression in renal adenocarcinoma ACHN cells (23).

PrP<sup>C</sup> can be found on the cell surface by attaching to the cell membrane and outside the cells being contained in exosomes which are secreted from the cells (67, 68). The secreted PrP<sup>C</sup> in tumor microenvironment binds to doxorubicin to prevent it from entering the nucleus and intercalating into DNA to induce cell death; and breast cancer patients with high levels of serum PrP<sup>C</sup> are at high risk of relapse following doxorubicin treatment (13). PrP synthetic peptide (amino acid residues 105 - 120 of the human prion protein) can protect schwannoma cells from H<sub>2</sub>O<sub>2</sub>-mediated cell death (29).

PrP<sup>C</sup> has been shown to protect cancer cells from apoptosis and autophagic cell death (69). PrP<sup>C</sup> inhibits apoptosis in neurons and in cancer cells (70). PrP<sup>C</sup> upregulation inhibits apoptosis induced by Bax expression, serum starvation and anti-cancer drug treatments (57, 70, 71). PrP<sup>C</sup> can bind to the C-terminus of the anti-apoptotic protein Bcl-2 to form a dimer inhibiting apoptosis (72). When PrP<sup>C</sup> is upregulated, Bcl-2/Bax ratio increases, resulting in anti-apoptosis in breast carcinoma MCF-7 cells (71). Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) is a ligand for death receptors which can induce cancer cell apoptosis (73). Downregulation of PrP<sup>C</sup> sensitizes adriamycin-resistant human breast cancer cells to TRAIL-induced apoptosis by increasing Bax/Bcl-2 ratio (58). PrP<sup>C</sup> inhibited TRAIL-induced apoptosis under hypoxia in human colon carcinoma cells (74). Akt was activated by PrP<sup>C</sup> to prevent TRAIL-induced apoptosis (75, 76). PrP<sup>C</sup> also activated PI3K/Akt signaling pathway contributing to its anti-Bax function by preventing the pro-apoptotic conformational changes of Bax at the early step of Bax activation (71). Moreover, PrP<sup>C</sup> protected lung and pancreatic cancer cells from apoptosis through downregulation of unfolded protein response (UPR) (77).

Autophagy is an evolutionarily conserved catabolic process in eukaryotic cells, in which unnecessary or dysfunctional cytosolic components are degraded and recycled through lysosomes (78). During autophagy (macroautophagy), cytosolic components (cargos) are surrounded by a phagophore which will expands and encloses to form the characteristic double-membraned structure autophagosome. Then, autophagosome will fuse with the lysosome to form autolysosome where cargos are degraded to generate small molecules that can be used for biosynthesis and energy production for cell survival, under stress conditions such as starvation (79). However, when autophagy is over-enhanced, it can induce cell death (autophagic cell death/autophagy-induced cell death) (79). Barbieri et al. demonstrated for the first time that PrP<sup>C</sup> can modulate autophagic cell death in glial tumor cells (80). They demonstrated that PrP<sup>C</sup> silencing resulted in inhibition of Mammalian target of rapamycin (mTOR) kinase activity in T98G glioma cells, promoting autophagy leading to autophagic cell death (80). Furthermore, PrP<sup>C</sup> inhibited autophagy by activating the antioxidant enzyme SOD (81). Since autophagy is mainly a pro-cell survival mechanism, it is expected that PrP<sup>C</sup> may antagonize drug resistance by inhibiting autophagy in cancer cells.
One study showed that tumor resistance to radiotherapy was also associated with the increased PrP<sup>C</sup> (82). In neuroblastoma, breast, and colorectal cancer cell lines, ionizing radiation (IR) can increase the expression of PrP<sup>C</sup> by activating ATM-TAK1-PrP<sup>C</sup> pathway, thereby leading to the resistance to radiotherapy of tumor cells (82). Taken together, PrP<sup>C</sup> can modulate various signaling pathways contributing to cancer drug resistance (Figure 3).

Although the overexpression of PrP<sup>C</sup> in cancer cells results in therapy-resistance, researchers have taken advantage of this characteristic to synthesize PrP<sup>C</sup>-Apt-functionalized doxorubicin-oligomer-AuNPs (PrP<sup>C</sup>-AptDOa) which could target PrP<sup>C</sup>-overexpressed CRC (83). PrP<sup>C</sup>-AptDOa inhibited CRCs proliferation and induced apoptosis more significantly than free Dox at the cellular level (83). However, PrP<sup>C</sup> is also expressed in normal cells, such as neurons and neuroglia. Therefore, the challenge for cancer treatment is to specifically target PrP<sup>C</sup> in cancer cells. In addition, further studies of PrP<sup>C</sup>-AptDOa should be conducted in an animal model and clinical trials to clarify its therapeutic effects and side effects on individuals.

**PrP<sup>C</sup> PROMOTES CANCER STEM CELL DEVELOPMENT**

Cancer stem cells (CSCs) are a small subpopulation of cancer cells with the capacities of self-renewal, differentiation and tumorigenicity (84). PrP<sup>C</sup> is engaged in different types of stem cells, such as hematopoietic stem cells (HSCs), gland stem cells, bone marrow-derived human mesenchymal stem cells (MSCs) and human embryonic stem (ES) cells (85–88). Studies have indicated that PrP<sup>C</sup> is also involved in CSCs. PrP<sup>C</sup> protected Oct4, a marker of colon cancer stem cells, from degradation by inducing heat shock protein 1 like (HSPA1L) when in response to co-treatment with 5-FU and melatonin (48). One study indicated that PrP<sup>C</sup> was highly expressed in consensus molecular subgroup (CMS4), a subtype of CRC with higher malignancy, and affected the prognosis of CRC as an upstream molecule in the PrP<sup>C</sup>-ILK-IDO1 axis (89). PrP<sup>C</sup> promoted EMT of colorectal cancer stem cells via activation of the ERK2 (MAPK1) pathway to increase cell metastasis (46). CD44 is a CSC marker and critical regulator of cancer stemness (90). PrP<sup>C</sup> is co-expressed with CD44 in colorectal CSCs (46). PrP<sup>C</sup> and Hsp70/90 organizing protein (HOP) acted together to regulate self-renewal, proliferation and migration in glioblastoma (GBM) stem-like cells (26). Downregulation of PrP<sup>C</sup> decreased stem cell-like properties of human GBM CSCs (91). Downregulation of PrP<sup>C</sup> in models of prion disease through immune, genetic and other mechanisms has achieved some progress. Application of anti-PrP antibodies have been proposed as a promising treatment many decades ago (92, 93). A recent study reported that transgenic mice expressing elk PrP (TgElk) benefited from active PrP vaccination (94). Minikel et al.
demonstrated that PrP-lowering antisense oligonucleotides (ASOs) worked via an RNAase-H dependent mechanism and has certain therapeutic effect on prion-infected mice (95). Minikel et al. also proposed that loss-of-function variant of Prnp could be potential targets for prion disease inhibitory drugs (96). The application of these PrP<sup>C</sup>-lowering approaches may provide novel cancer therapies by targeting CSCs.

**CONCLUSION**

Prion protein (PrP) is expressed in nervous system and other organs (97). There are two forms of PrP, including normal PrP<sup>C</sup> and disease causing PrP<sup>C</sup>. PrP<sup>C</sup> misfolding and aggregation can cause fatal neurodegenerative conditions (98). Studies in recent years show that it also plays a role in cancer. PrP<sup>C</sup> can stimulate cancer progression by promoting cancer cell proliferation, invasion/metastasis, drug resistance, and cancer stem cell development. Therefore, targeting PrP<sup>C</sup> is a novel approach for cancer treatment.

**AUTHOR CONTRIBUTIONS**

MD and YC conceived the topic and designed the outline of this review. MD contributed to the manuscript writing and prepared the figures and tables. YC modified the language. LC, YC and YL critically revised the manuscript. All authors contributed to the article and approved the submitted version.

**FUNDING**

This work was supported by a grant from the National Natural Science Foundation of China (82071351).

**REFERENCES**

1. Atkinson CJ, Zhang K, Munn AL, Wiegmans A, Wei MQ, Prion Protein Scarpie and the Normal Cellular Prion Protein. *Prior* (2016) 10(1):63–82. doi: 10.1080/19336886.2015.1110293
2. Prion SA, Chesebro B, Caughey B. Biomedicine. A View From the Top–Prion Diseases From 10,000 Feet. *Sci (N Y NY)* (2003) 300(5621):917–9. doi: 10.1126/science.1085920
3. Soto C, Satani N. The Intricate Mechanisms of Neurodegeneration in Prion Diseases. *Trends Mol Med* (2011) 17(1):14–24. doi: 10.1016/j.ymmed.2010.09.001
4. Westergard L, Christensen HM, Harris DA. The Cellular Prion Protein (PrP (C)): Its Physiological Function and Role in Disease. *Biochim Biophys Acta* (2007) 1772(6):629–44. doi: 10.1016/j.bbadis.2007.02.011
5. Harris DA. Trafficking, Turnover and Membrane Topology of PrP. *Br Med Bull* (2003) 66:71–85. doi: 10.1093/bmb/lhd61.171
6. Linden R, Cordeiro Y, Lima LMTR. AllostERIC Function and Dysfunction of the Prion Protein. *Cell Mol Life Sci CMLS* (2012) 69(7):1105–24. doi: 10.1007/s00018-011-0847-7
7. Alves RN, Iglesia RP, Prado MB, Melo Escobar MI, Boccacino JM, Fernandes CFL, et al. A New Take on Prion Protein Dynamics in Cellular Trafficking. *Int J Mol Sci* (2020) 21(20):7763. doi: 10.3390/ijms21207763
8. Stahl N, Borchelt DR, Hsiao K, Prusiner SB. Scrapie Prion Protein Contains a Phosphatidylinositol Glycolipid. *Cell* (1987) 51(2):229–40. doi: 10.1016/0022-8674(87)90150-4
9. Naaslavsky N, Stein R, Yanai A, Friedlander G, Taraboulos A. Characterization of Detergent-Insoluble Complexes Containing the Cellular Prion Protein and its Scarpie Isoform. *J Biol Chem* (1997) 272(10):6324–31. doi: 10.1074/jbc.272.10.6324
10. Fioriti L, Dossena S, Stewart LR, Stewart RS, Harris DA, Forloni G, et al. Cytosolic Prion Protein (PrP(Sc)) Is Not Toxic in N2a Cells and Primary Neurons Expressing Pathogenic PrP Mutations. *J Biol Chem* (2005) 280(12):11320–8. doi: 10.1074/jbc.M412441200
11. Díey M-A, Jodon J, Ursini-Siegel J, Aleynikova O, Ferrario C, Hassan S, et al. Endoplasmic Reticulum Stress Induces PRNP Prion Protein Gene Expression in Breast Cancer. *Breast Cancer Res BCR* (2013) 15(2):R22–R. doi: 10.1186/bcr3398
12. Morel E, Fouquet S, Strup-Perrot C, Pichol Thievend C, Petit C, Loew D, et al. The Cellular Prion Protein PrP(C) Is Involved in the Proliferation of Erithelial Cells and in the Distribution of Junction-associated Proteins. *PloS One* (2008) 3(8):e3000–e. doi: 10.1371/journal.pone.0003000
13. Wiegmans AP, Saunus JM, Ham S, Lobb R, Kutjasovic JR, Dalley AJ, et al. Secreted Cellular Prion Protein Binds Doxorubincin and Correlates With Anthracycyline Resistance in Breast Cancer. *JCI Insight* (2019) 5(6):e124092. doi: 10.1172/jci.insight.124092
14. Santos TG, Lopes MH, Martins VR. Targeting Prion Protein Interactions in Cancer. *Prior* (2015) 9(3):165–73. doi: 10.1080/19336886.2015.1027855
15. Mehrpour M, Codogno P. Prion Protein: From Physiology to Cancer Biology. *Cancer Lett* (2010) 290(1):1–23. doi: 10.1016/j.canlet.2009.07.009
16. Tang Z, Ma J, Zhang W, Gong C, He J, Wang Y, et al. The Role of Prion Protein Expression in Predicting Gastric Cancer Prognosis. *J Cancer* (2016) 7(8):984–90. doi: 10.7150/jca.14237
17. Kim J-I, Cali I, Sureauwicz K, Kong Q, Raymond GJ, Atarashi R, et al. Mammalian Prions Generated From Bacterially Expressed Prion Protein in the Absence of Any Mammalian Cofactors. *J Biol Chem* (2010) 285(19):14083–7. doi: 10.1074/jbc.C110.113464
18. Wang Q, Qian J, Wang F, Ma Z. Cellular Prion Protein Accelerates Colorectal Cancer Metastasis via the Fyn-SPI1-SATB1 Axis. *Oncol Rep* (2012) 28(6):2029–34. doi: 10.3892/or.2012.2025
19. Singh A, Settleman J. EMT, Cancer Stem Cells and Drug Resistance: An Emerging Axis of Evil in the War on Cancer. *Oncogene* (2010) 29(34):4741–51. doi: 10.1038/onc.2010.215
20. Duffy MJ, Maguire TM, Hill A, McDermott E, O’Higgins N. Metalloproteinases: Role in Breast Carcinogenesis, Invasion and Metastasis. *Breast Cancer Res BCR* (2000) 2(4):252–7. doi: 10.1186/bcr56
21. Medema JP. Cancer Stem Cells: The Challenges Ahead. *Nat Cell Biol* (2013) 15(4):338–44. doi: 10.1038/nchb2717
22. Liang J, Pan Y, Zhang D, Guo C, Shi Y, Wang J, et al. Cellular Prion Protein Promotes Proliferation and G1/S Transition of Human Gastric Cancer Cells SGC7901 and AGS. *FASEB J Off Publ Fed Am Soc Exp Biol* (2007) 21(9):2247–56. doi: 10.1096/fj.06-7799com
23. Yap Y-H, Say Y-H. Resistance Against Tumour Necrosis Factor α. Apoptosis by the Cellular Prion Protein Is Cell-Specific for Oral, Colon and Kidney Cancer Cell Lines. *Cell Biol Int* (2012) 36(3):273–7. doi: 10.1002/cbi.2010088
24. Yun CW, Yun S, Lee JH, Han Y-S, Yoon YM, An D, et al. Silencing Prion Protein in HT29 Human Colorectal Cancer Cells Enhances Anticancer Response to Fucoidan. *Anticancer Res* (2016) 36(9):4449–58. doi: 10.21873/anticancer.10989
25. Lopes MH, Santos TG, Rodrigues BR, Queiroz-Hazarbassanov N, Cunha IW, Wasilewska-Sampaio AP, et al. Disruption of Prion Protein-HOP Engagement Impairs Glioblastoma Growth and Cognitive Decline and Improves Overall Survival. *Oncogene* (2015) 34(25):3305–14. doi: 10.1038/onc.2014.261
26. Iglesia RP, Prado MB, Cruz L, Martins VR, Santos TG, Lopes MH. Engagement of Cellular Prion Protein With the Co-Chaperone Hsp70/90 Organizing Protein Regulates the Proliferation of Glioblastoma Stem-Like Cells. *Stem Cell Res Ther* (2017) 8(1):76. doi: 10.1186/s13287-017-0518-1
27. Warburg O. The Metabolism of Carcinoma Cells. *J Cancer Res* (1925) 9:148–63. doi: 10.1158/jcr.1925.148

Frontiers in Oncology | www.frontiersin.org September 2021 Volume 11 Article 742949 6
68. Lewis V, Johansson VA, Crouch PJ, Klug GM, Hooper NM, Collins SJ. Prion Protein “Gemma-Cleavage”: Characterizing a Novel Endoproteolytic Processing Event. Cell Mol Life Sci CMLS (2016) 73(3):667–83. doi: 10.1007/s00018-015-2022-z

69. Yang X, Zhang Y, Zhang L, He T, Zhang J, Li C. Prion Protein and Cancers. Acta Biochim Biophys Sin (Shanghai) (2014) 46(6):431–40. doi: 10.1093/abbs/gnu019

70. Kuwahara C, Takeuski AM, Nishimura T, Haraguchi K, Kuboaki S, Matsumoto Y, et al. Prions Prevent Neuronal Cell-Line Death. Nature (1999) 400(6741):225–6. doi: 10.1038/22241

71. Roucou X, Giannopoulos PN, Zhang Y, Jodoin J, Goodyer CG, LeBlanc A. Cellular Prion Protein Inhibits Proapoptotic Bax Conformational Change in Human Neurons and in Breast Carcinoma MCF-7 Cells. Cell Death Differentiation (2005) 12(7):783–95. doi: 10.1038/sj.cdd.4401629

72. Kurschner C, Morgan JL. Analysis of Interaction Sites in Homo- and Heteromeric Complexes Containing Bc1-2 Family Members and the Cellular Prion Protein. Brain Res Mol Brain Res (1996) 37(1-2):249–58. doi: 10.1016/0169-328x(95)00323-k

73. Wiley SR, Schooley K, Smolak P, Din WS, Huang CP, Nicholl JK, et al. Identification and Characterization of a New Member of the TNF Family That Induces Apoptosis. Immunity (1995) 3(6):673–82. doi: 10.1016/1074-7613(95)90057-8

74. Park J-Y, Jeong J-K, Lee J-H, Moon J-H, Lee J-Y, et al. Induction of Cellular Prion Protein (PrP*) Under Hypoxia Inhibits Apoptosis Caused by TRAIL Treatment. Oncotarget (2015) 6(7):5342–53. doi: 10.18632/oncotarget.3028

75. Xu J, Zhou Y-F, Wei W-Z, Wu GS. Activation of the Akt Survival Pathway Contributes to TRAIL Resistance in Cancer Cells. PloS One (2010) 5(4):e10226-e. doi: 10.1371/journal.pone.0010226

76. Ramlijak S, Herlyn H, Zerr I. Cellular Prion Protein (PrP*) and Hypoxia: True Friends to Each Other in Good Times and in Bad, in Sickness, and in Health. Front Cell Neurosci (2016) 10:292. doi: 10.3389/fncel.2016.00292

77. Gao Z, Peng M, Chen L, Yang X, Li H, Shi R, et al. Prion Protein Protects Cancer Cells Against Endoplasmic Reticulum Stress Induced Apoptosis. Virol Sin (2019) 34(2):222–34. doi: 10.1007/s12250-019-00107-2

78. Allirezai M, Kembell CC, Flynn CT, Wood MR, Whitlon JL, Kisses WB. Short-Term Fasting Induces Profound Neuronal Autophagy. Autophagy (2010) 6(6):702–10. doi: 10.4161/auto.6.6.12376

79. Chen Y, Klionsky DJ. The Regulation of Autophagy - Unanswered Questions. J Cell Sci (2011) 124(Pt 2):161–70. doi: 10.1242/jcs.064576

80. Barbieri G, Palumbo S, Gabrusiewicz K, Azzalin A, Marchesi N, Spedito A, et al. Silencing of Cellular Prion Protein (PrP*) Expression by DNA-Antisense Oligonucleotides Induces Autophagy-Dependent Cell Death in Glioma Cells. Autophagy (2011) 7(8):840–53. doi: 10.4161/auto.7.8.15615

81. Oh J-M, Choi E-K, Carpenter RI, Kim Y-S. Oxidative Stress Impairs Autophagic Flux in Prion Protein-Deficient Hippocampal Cells. Autophagy (2012) 8(10):1448–60. doi: 10.4161/auto.21164

82. Bernardino-Sgherri J, Sibercioti C, Avrue F, Busso D, Brocas C, El Masri G, et al. Tumor Resistance to Radiotherapy Is Triggered by an ATM/TAK1-Interacting Protein That Inhibits Autophagy. Oncogene (2020) 40(19):633–58. doi: 10.1186/s41586-020-2267-z

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher’s Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.