BMB
Reports

BMB Rep. 2023; 56(12): 645-650
www.bmbreports.org

Contributed Mini Review

The role of cellular prion protein in immune system

*Seunghwa Cha & Mi-Yeon Kim**
Department of Bioinformatics and Life Science, Soongsil University, Seoul 06978, Korea

Numerous studies have investigated the cellular prion protein (PrP^C) since its discovery. These investigations have explained that its structure is predominantly composed of alpha helices and short beta sheet segments, and when its abnormal scrapie isoform (PrP^{Sc}) is infected, PrP^{Sc} transforms the PrP^C, leading to prion diseases, including Creutzfeldt-Jakob disease in humans and bovine spongiform encephalopathy in cattle. Given its ubiquitous distribution across a variety of cellular types, the PrP^C manifests a diverse range of biological functions, including cell-cell adhesion, neuroprotection, signalings, and oxidative stress response. PrP^C is also expressed in immune tissues, and its functions in these tissues include the activation of immune cells and the formation of secondary lymphoid tissues, such as the spleen and lymph nodes. Moreover, high expression of PrP^C in immune cells plays a crucial role in the pathogenesis of prion diseases. In addition, it affects inflammation and the development and progression of cancer via various mechanisms. In this review, we discuss the studies on the role of PrP^C from various immunological perspectives. [BMB Reports 2023; 56(12): 645-650]

INTRODUCTION

The cellular prion protein (PrP^C) is predominantly found in the brain tissue and neurons, where it is attached to the cell membrane (1-3). PrP^C is a single polypeptide composed of 208 amino acids in mice and 209 amino acids in humans (4-6). In the human PrP^C, there are two N-glycosylation sites located at residue 181 and 197. Through Western blotting, diglycosylated (36 kDa), monoglycosylated (33 kDa), and unglycosylated cerebral PrP isoforms (27 kDa) can be distinguished (7, 8). PrP^C exhibits a predominantly alpha-helical structure with a flexible N-terminal domain and a globular C-terminal domain. The C-terminal region contains three alpha helices and two short segments of the beta sheet structure. For its abnormal scrapie isoform (PrP^{Sc}), PrP^C undergoes a conformational change that converts alpha helices into beta-sheets (6, 9, 10). This conformational alteration is associated with the pathogenicity and transmission of prion diseases (3, 11-13). Prion diseases, also known as transmissible spongiform encephalopathies, are rare and fatal neurodegenerative disorders that are caused by the accumulation of abnormally folded PrP^{Sc} in the brain of humans and animals (14-16). The abnormal PrP^{Sc} form acts as a template and induces the conversion of PrP^C into a disease-associated form. This results in progressive accumulation of PrP^{Sc}, which disrupts normal brain function and causes neuronal damage (17-19). Based on the specific type and region of the brain affected, prion diseases manifest with different symptoms, including cognitive impairment, memory loss, behavioral changes, movement disorders, and severe neurological dysfunction (20, 21). Several prion diseases affect humans, including Creutzfeldt-Jakob disease (CJD), variant CJD, Gerstmann-Sträussler-Scheinker syndrome, and fatal familial insomnia (22, 23). Each disease has distinct clinical and pathological features.

PrP^C plays multifaceted roles in various cellular processes, including cell-cell adhesion (24), neuroprotection (25, 26), intracellular signaling (27), cell death and survival (28), and oxidative stress response (29). In addition to nerve cells, PrP^C is also expressed in various other cells, especially leukocytes, which are a part of the immune system (30). Despite the high expression of PrP^C in leukocytes, there have been limited scientific investigations of its precise role of PrP^C.

Here, we provide an overview of the studies investigating the role of PrP^C in the immune system. Specifically, we discuss the expression of PrP^C in immune cells and its function in the structural formation of secondary lymphoid tissues, such as the spleen and lymph nodes. Furthermore, we focused on the mechanisms of peripheral PrP^{Sc} replication and neuroinvasion of PrP^{Sc} via the immune system. We also examined the involvement of PrP^C in inflammation, cancer development, and metastasis.

EXPRESSION OF PrP^C ON IMMUNE CELLS

PrP^C is widely expressed on cell surfaces at different levels in immune cells, such as T lymphocytes (31, 32), natural killer (NK) cells (33, 34), macrophages (35), dendritic cells (DCs) (36), regulatory T cells (37) and follicular dendritic cells (FDCs)

*Corresponding author. Tel: +82-2-820-0458; Fax: +82-2-824-4383; E-mail: kimmy@ssu.ac.kr

https://doi.org/10.5483/BMBRep.2023-0151

Received 17 August 2023, Revised 13 September 2023, Accepted 25 September 2023, Published online 14 November 2023

Keywords: Cancer, Immune system, Inflammation, Prion, Prion disease

ISSN: 1976-670X (electronic edition)

(38). Although the role of PrP^C in immune cells is not well understood, PrP^C expression increases during NK cell differentiation and functional maturation (33, 34). In addition, PrP^C in human T cells interacts with the transducer protein zeta-chain associated protein-70, which plays a critical role in the signaling pathway leading to T cell activation (31). Elevated levels of PrP^C expression have been found to facilitate T lymphocyte activation, promote cell proliferation, and enhance differentiation through the T cell receptor signaling pathway (32). DCs also exhibit upregulation of PrP^C expression after maturation (36). PrP^C also affects the phagocytic capacity of macrophages by activating the ERK1/2 and Akt kinases (35). Taken together, these studies demonstrate a correlation between the activation of immune cells and PrP^C expression, although the exact role of upregulated PrP^C remains uncertain.

Regulatory T cells, known for their ability to suppress immune responses, express higher levels of PrP^C than conventional T cells (37). Our recent study showed that PrP^C is involved in the development and function of regulatory T cells and it will be discussed in detail in section 'Role of regulatory T cells in cancer and their relationship with PrP^C.'

FDCs are a specialized type of non-hematopoietic immune cell found primarily within the B cell area of secondary lymphoid tissues and are recognized for their high expression of PrP^C. During infection with PrP^{Sc}, they serve as the initial sites of accumulation in the lymphoid tissues before PrP^{Sc} subsequently spreads to the central nervous system (CNS) (38). However, specific ablation of PrP^C expression in FDCs using Cre-mediated recombination did not affect the normal function of FDCs (39). Further studies are required to elucidate the functions of PrP^C in FDCs.

INVOLVEMENT OF PrP^C IN THE STRUCTURE OF SECONDARY LYMPHOID TISSUES

To investigate the role of PrP^C in the structure and organization of secondary lymphoid tissues, such as the spleen and lymph nodes, several studies have been performed using mice lacking PrP^C ($Prnp^{0/0}$) and mice infected with the mouse-adapted scrapie strain ME7 (40-42). These studies revealed that PrP^C plays an important role in the formation and maintenance of secondary lymphoid tissue structures. Spleen obtained from $Prnp^{0/0}$ and ME7-infected mice showed impaired structures, with a lack of segregation between the T and B zones in the white pulp region. In both cases, there was no or significant reduction in the size of the T-zone. This can be attributed to the decreased expression of T-cell homing chemokines CCL19 and CCL21, which are involved in T-zone formation (43), leading to impaired recruitment of CD4 T cells in both mouse models (40, 41). Although both $Prnp^{0/0}$ and ME7-infected spleens exhibited impaired T-zone structures, when compared to uninfected wild-type mice, the number of lymphoid tissue inducer (LTi) cells, which are important for secondary lymphoid tissue development (44, 45) decreased in $Prnp^{0/0}$ spleens but remained unchanged in ME7-infected spleens. These results suggest that persistent PrP^C, without conversion to PrP^{Sc} in ME7-infected mice likely regulates both the quantity of LTi cells and their migration to the spleen.

PATHOGENESIS OF PRION DISEASES VIA IMMUNE SYSTEM

Prion diseases develop when PrP^{Sc} infects the host. Infected PrP^{Sc} continuously converts PrP^C to PrP^{Sc}, leading to the accumulation of PrP^{Sc}. Ultimately, the accumulation of PrP^{Sc} leads to the onset of prion diseases (46, 47). PrP^{Sc} accumulation primarily occurs in the immune system as immune cells express PrP^C (47-49). Following infection, PrP^{Sc} circulates through the bloodstream and reaches secondary lymphoid tissues such as the lymph nodes, tonsils, Peyer's patches, and spleen. At these sites, PrP^{Sc} utilizes immune cells to replicate and accumulate (46, 50). Once sufficient replication and accumulation occur, prion diseases are triggered subsequent to CNS infection, initiating the progression of pathological manifestations. Therefore, PrP^{Sc} accumulation in the secondary lymphoid tissues is crucial for movement of PrP^{Sc} into the CNS.

FDCs found in the B cell area of germinal centers (GCs) in secondary lymphoid tissues are critical for capturing naïve antigens using FcγRIIB and complement receptors and presenting them to GC B cells (51-53). In response to these antigens, B cells receive help from follicular helper T (Tfh) cells, which leads to their activation and subsequent differentiation into plasma cells (54-56). Due to high PrP^C expression levels, FDCs accumulate considerable amount of PrP^{Sc} upon infection. Consequently, FDCs are pivotal in the onset of prion diseases, and the spleen serves as the primary site for PrP^{Sc} replication mediated by FDCs (57-60). In the absence of FDCs, the lack of a site for accumulation of PrP^{Sc} prevents its accumulation. Consequently, neuroinvasion does not occur in the absence of PrP^{Sc} accumulation (60-62).

Our study showed that ME7-infected mice exhibited increased FDC networks and Tfh cell responses, which persisted throughout the progression of prion disease (42). Despite a decrease in CD4 T cells in the white pulp, there was an increase in CD4 T cells within GCs, accompanied by higher expression levels of Tfh-related genes, such as Bcl6, Il21, Cxcr5, Icos, and Pdcd1. Moreover, the ME7-infected spleens showed an elevated number of CD4 memory T cells. These results suggest that although ME7 infection led to an impaired structure in the splenic white pulp, there was an expansion of CD4 memory T cells and prolonged Tfh cell responses necessary to support the replication and accumulation of PrP^{Sc} within GCs.

ROLE OF PrP^C IN INFLAMMATION

Several studies have investigated the effects of PrP^C on inflammatory responses, given its substantial expression in im-

mune cells and its ability to influence immune cell activation and recruitment. These studies revealed that PrP^C protects organs from inflammatory responses through its immunomodulatory function (63-67). High expression of PrP^C in immune-privileged organs, including the brain, placenta, eyes, testes, and uterus, serves as a protective mechanism against inflammation-induced damage to these organs (63). Inflammation studies using *Prnp*-knockout models have been conducted to investigate the protective role of PrP^C against inflammation (68-71). Tsutsui *et al*. demonstrated that $Prnp^{0/0}$ mice immunized with myelin oligodendrocyte glycoprotein peptide to induce experimental autoimmune encephalomyelitis exhibited a more aggressive disease onset characterized by higher levels of leukocytic infiltrates and increased expression of pro-inflammatory cytokine genes in the brain and spinal cord suggesting the protective role of PrP^C against neuroinflammation (68). Petit *et al*. investigated the severity of inflammatory bowel disease induced by dextran sodium sulfate and found that mice lacking PrP^C exhibited more severe symptoms than wild-type mice (69). Furthermore, when PrP^C was knocked down in human enterocytes, there was a decrease in cell-cell junctions. The weakening of the intestinal barrier, consisting of tight cell-cell junctions, can lead to vulnerability to external invasion and infection, potentially resulting in inflammatory bowel diseases such as Crohn's disease and ulcerative colitis. Consistent with these findings, patients with Crohn's disease or ulcerative colitis showed decreased levels of PrP^C at cell-cell junctions in the colonic epithelia (69). Taken together, these results revealed that in the absence of PrP^C, there was an increase in inflammatory responses and a greater extent of associated damage.

In another study, goats lacking PrP^C exhibited prolonged symptoms in response to lipopolysaccharide-induced (LPS)-induced systemic inflammation (70). In another study using LPS, Liu *et al*. showed that upon LPS injection, wild-type mice exhibited elevated levels of pro-inflammatory cytokines in the brain and spleen during the acute phase, whereas $Prnp^{0/0}$ mice displayed lower cytokine levels (71). Additionally, $Prnp^{0/0}$ mice showed higher mortality rates in response to LPS-induced septic shock. These results suggest that PrP^C plays a crucial role in protecting against LPS injection by modulating the inflammatory response.

ROLE OF PrP^C IN CANCER DEVELOPMENT AND METASTASIS

Several studies have demonstrated that PrP^C stimulates cancer cell proliferation through various mechanisms. Elevated levels of PrP^C expression have been linked to unfavorable prognoses and have been observed in various human cancers such as gastric carcinoma (72), renal adenocarcinoma (73), colorectal cancer (74, 75), breast cancer (76, 77), and melanoma (78). In gastric cancer cells, PrP^C overexpression activates the phosphatidylinositide 3-kinase pathway and upregulation of cyclin D1, promoting the G1/S phase transition and consequently facilitating cell proliferation (79). Another study reported that PrP^C influences the G1/S phase transition in several renal adenocarcinoma cell lines (80). Consistent with these findings, in the absence of PrP^C, the expression of cyclins and cyclin-dependent kinases is suppressed, leading to the inhibition of cell proliferation in colon cancer (81).

Gil *et al*. demonstrated that PrP^C contributes to the invasion and migration of breast cancer cells by regulating matrix metalloprotease-9 (MMP-9) (82). They showed that overexpression of PrP^C in the breast cancer cell line MCF-7 leads to an increase in MMP-9 expression by enhancing the association of NF-κB with the promoter region of the MMP-9 gene and activating the ERK signaling pathway. Conversely, when PrP^C is silenced using siRNA, a notable decrease in ERK activation and MMP-9 expression is observed, leading to the suppression of cell migration and invasion (82).

Reportedly, PrP^C plays a role in both cancer development and metastasis, the process by which cancer cells spread from the primary tumor to other parts of the body (72, 83, 84). Metastatic gastric cancers exhibit high PrP^C expression, which plays a substantial role in enhancing the adhesive, invasive, and metastatic capacities of gastric cancer cell lines (72). According to Pan *et al*., the N-terminal region of PrP^C can activate the MEK/ERK pathway, ultimately leading to transactivation of MMP11. This activation enhances the invasive and metastatic properties of gastric cancer cells, indicating their potential role in promoting metastasis (72). Additionally, the overexpression of MMP11 is frequently associated with a more aggressive tumor phenotype and resistance to apoptosis (83). Wang *et al*. showed that PrP^C is specifically expressed at the invasive front of colorectal cancers (CRCs), promoting tumor invasion through the acquisition of characteristics associated with epithelial-mesenchymal transition (84). Additionally, they showed that knockdown of PrP^C in an orthotopic xenograft model significantly reduced the number of distant metastases, supporting the significant role of PrP^C in the regulation of CRC progression and metastasis.

ROLE OF REGULATORY T CELLS IN CANCER AND THEIR RELATIONSHIP WITH PrP^C

Research on the role of PrP^C in cancer invasion and metastasis has revealed its association with regulatory T cells (37, 78). Regulatory T cells possess immunosuppressive functions and exhibit elevated activity in numerous types of cancers (85, 86). An increased number of tumor-infiltrating regulatory T cells have been identified, and their increased activity are observed in various human cancers, including liver, lung, breast, gastrointestinal tract, pancreas, and ovarian cancers (85-87). Our recent study showed that when B16F10 melanoma cells were injected into $Prnp^{0/0}$ and PrP-overexpressing (Tga20) mice to induce lung metastasis, Tga20 mice reached the terminal stage much faster than $Prnp^{0/0}$ mice as lung metastasis occurred (78).

This effect was likely associated with an increased number of regulatory T cells. The expression of transforming growth factor-beta (TGF-β) and programmed death ligand-1 (PD-L1), which play important roles in the differentiation and function of regulatory T cells, was upregulated in Tga20 mice compared with $Prnp^{0/0}$ mice. These results suggest that during the invasion and metastasis of cancer cells, PrP^C may contribute to the development and activation of regulatory T cells by increasing the expression of TGF-β and PD-L1, which enhances their functionality.

CONCLUSION

In almost all cells, PrP^C is expressed, participating in diverse cellular processes and also found in immune cells, suggesting potential roles in the immune system. Based on the research findings to date, it has been revealed that PrP^C has a protective function in inflammatory responses triggered by infections, but contributes to the development of cancer through various mechanisms, including regulation of cell proliferation, enhancement of adhesive, invasive, and metastatic capacities, and boosting regulatory T cell activation. These findings suggest that PrP^C plays a crucial role in the immune system and has substantial implications in the pathogenesis of conditions like inflammation and cancer. However, since much of this research is based on results of phenomena observed through knockout systems, further investigations are required to unveil the specific roles of PrP^C in individual immune cells, elucidate molecular mechanisms, and understand the interactions through which PrP^C influences the immune system. Future studies exploring the precise functions of PrP^C in the immune system will enable the regulation of the immune system using PrP^C, which can be applied for the treatment of various diseases.

ACKNOWLEDGEMENTS

This work was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF), funded by the Ministry of Education, Science, and Technology (NRF- 2016R1D1A1B01011371).

CONFLICTS OF INTEREST

The authors have no conflicting interests.

REFERENCES

1. Mabbott NA, Brown KL, Manson J and Bruce ME (1997) T-lymphocyte activation and the cellular form of the prion protein. Immunology 92, 161-165
2. Antoine N, Cesbron JY, Coumans B, Jolois O, Zorzi W and Heinen E (2000) Differential expression of cellular prion protein on human blood and tonsil lymphocytes. Haematologica 85, 475-480
3. Stahl N, Borchelt DR, Hsiao K and Prusiner SB (1987) Scrapie prion protein contains a phosphatidylinositol glycolipid. Cell 51, 229-240
4. Riek R, Hornemann S, Wider G, Glockshuber R and Wuthrich K (1997) NMR characterization of the full-length recombinant murine prion protein, mPrP(23-231). FEBS Lett 413, 282-288
5. Sparkes RS, Simon M, Cohn VH et al (1986) Assignment of the human and mouse prion protein genes to homologous chromosomes. Proc Natl Acad Sci U S A 83, 7358-7362
6. Zahn R, Liu A, Luhrs T et al (2000) NMR solution structure of the human prion protein. Proc Natl Acad Sci U S A 97, 145-150
7. Schmitz M, Lullmann K, Zafar S et al (2014) Association of prion protein genotype and scrapie prion protein type with cellular prion protein charge isoform profiles in cerebrospinal fluid of humans with sporadic or familial prion diseases. Neurobiol Aging 35, 1177-1188
8. Yang Y, Chen L, Pan HZ, Kou Y and Xu CM (2009) Glycosylation modification of human prion protein provokes apoptosis in HeLa cells in vitro. BMB Rep 42, 331-337
9. Damberger FF, Christen B, Perez DR, Hornemann S and Wuthrich K (2011) Cellular prion protein conformation and function. Proc Natl Acad Sci U S A 108, 17308-17313
10. Riesner D (2003) Biochemistry and structure of PrP(C) and PrP(Sc). Br Med Bull 66, 21-33
11. Pan KM, Baldwin M, Nguyen J et al (1993) Conversion of alpha-helices into beta-sheets features in the formation of the scrapie prion proteins. Proc Natl Acad Sci U S A 90, 10962-10966
12. Wille H and Requena JR (2018) The Structure of PrP(Sc) Prions. Pathogens 7, 20
13. Diaz-Espinoza R and Soto C (2012) High-resolution structure of infectious prion protein: the final frontier. Nat Struct Mol Biol 19, 370-377
14. Chesebro B (2003) Introduction to the transmissible spongiform encephalopathies or prion diseases. Br Med Bull 66, 1-20
15. Peggion C, Bertoli A and Sorgato MC (2017) Almost a century of prion protein(s): from pathology to physiology, and back to pathology. Biochem Biophys Res Commun 483, 1148-1155
16. Chen RJ, Chang WW, Lin YC, Cheng PL and Chen YR (2013) Alzheimer's amyloid-beta oligomers rescue cellular prion protein induced tau reduction via the Fyn pathway. ACS Chem Neurosci 4, 1287-1296
17. Nicotera P (2001) A route for prion neuroinvasion. Neuron 31, 345-348
18. Daude N (2004) Prion diseases and the spleen. Viral Immunol 17, 334-349
19. Wierzbicka A and Deptula W (2008) The role of the immune system in the pathogenesis of prion diseases. Postepy Hig Med Dosw (Online) 62, 166-173
20. Thompson A, MacKay A, Rudge P et al (2014) Behavioral and psychiatric symptoms in prion disease. Am J Psychiatry 171, 265-274
21. Kim HO, Snyder GP, Blazey TM, Race RE, Chesebro B and Skinner PJ (2008) Prion disease induced alterations in

gene expression in spleen and brain prior to clinical symptoms. Adv Appl Bioinform Chem 1, 29-50
22. Budka H, Aguzzi A, Brown P et al (1995) Neuropathological diagnostic criteria for Creutzfeldt-Jakob disease (CJD) and other human spongiform encephalopathies (prion diseases). Brain Pathol 5, 459-466
23. Kitamoto T, Muramoto T, Mohri S, Doh-Ura K and Tateishi J (1991) Abnormal isoform of prion protein accumulates in follicular dendritic cells in mice with Creutzfeldt-Jakob disease. J Virol 65, 6292-6295
24. Malaga-Trillo E, Solis GP, Schrock Y et al (2009) Regulation of embryonic cell adhesion by the prion protein. PLoS Biol 7, e55
25. Lopes MH, Hajj GN, Muras AG et al (2005) Interaction of cellular prion and stress-inducible protein 1 promotes neuritogenesis and neuroprotection by distinct signaling pathways. J Neurosci 25, 11330-11339
26. Doeppner TR, Kaltwasser B, Schlechter J et al (2015) Cellular prion protein promotes post-ischemic neuronal survival, angioneurogenesis and enhances neural progenitor cell homing via proteasome inhibition. Cell Death Dis 6, e2024
27. Lee YJ and Baskakov IV (2014) The cellular form of the prion protein guides the differentiation of human embryonic stem cells into neuron-, oligodendrocyte-, and astrocyte-committed lineages. Prion 8, 266-275
28. Bravard A, Auvre F, Fantini D et al (2015) The prion protein is critical for DNA repair and cell survival after genotoxic stress. Nucleic Acids Res 43, 904-916
29. Kouadri A, El Khatib M, Cormenier J et al (2019) Involvement of the prion protein in the protection of the human bronchial epithelial barrier against oxidative stress. Antioxid Redox Signal 31, 59-74
30. Isaacs JD, Jackson GS and Altmann DM (2006) The role of the cellular prion protein in the immune system. Clin Exp Immunol 146, 1-8
31. Mattei V, Garofalo T, Misasi R et al (2004) Prion protein is a component of the multimolecular signaling complex involved in T cell activation. FEBS Lett 560, 14-18
32. Li R, Liu D, Zanusso G et al (2001) The expression and potential function of cellular prion protein in human lymphocytes. Cell Immunol 207, 49-58
33. Durig J, Giese A, Schulz-Schaeffer W et al (2000) Differential constitutive and activation-dependent expression of prion protein in human peripheral blood leucocytes. Br J Haematol 108, 488-495
34. Dodelet VC and Cashman NR (1998) Prion protein expression in human leukocyte differentiation. Blood 91, 1556-1561
35. Krebs B, Dorner-Ciossek C, Schmalzbauer R, Vassallo N, Herms J and Kretzschmar HA (2006) Prion protein induced signaling cascades in monocytes. Biochem Biophys Res Commun 340, 13-22
36. Martinez del Hoyo G, Lopez-Bravo M, Metharom P, Ardavin C and Aucouturier P (2006) Prion protein expression by mouse dendritic cells is restricted to the nonplasmacytoid subsets and correlates with the maturation state. J Immunol 177, 6137-6142
37. Isaacs JD, Garden OA, Kaur G, Collinge J, Jackson GS and Altmann DM (2008) The cellular prion protein is preferentially expressed by CD4+ CD25+ Foxp3+ regulatory T cells. Immunology 125, 313-319
38. McCulloch L, Brown KL, Bradford BM et al (2011) Follicular dendritic cell-specific prion protein (PrP) expression alone is sufficient to sustain prion infection in the spleen. PLoS Pathog 7, e1002402
39. McCulloch L, Brown KL and Mabbott NA (2013) Ablation of the cellular prion protein, PrPC, specifically on follicular dendritic cells has no effect on their maturation or function. Immunology 138, 246-257
40. Kim S, Han S, Lee YE et al (2016) Prion protein-deficient mice exhibit decreased CD4 T and LTi cell numbers and impaired spleen structure. Immunobiology 221, 94-102
41. Kim S, Han S, Lee HS, Kim YS, Choi EK and Kim MY (2016) Impaired spleen structure and chemokine expression in ME7 scrapie-infected mice. Immunobiology 221, 871-878
42. Kim S, Han S, Kim T et al (2018) Prolonged follicular helper T cell responses in ME7 scrapie-infected mice. Prion 12, 109-116
43. Fevang B, Yndestad A, Damas JK et al (2009) Chemokines and common variable immunodeficiency; possible contribution of CCL19, CCL21 and CCR7 to immune dysregulation. Clin Exp Immunol 158, 237-245
44. Kim MY, Gaspal FM, Wiggett HE et al (2003) CD4(+) CD3(−) accessory cells costimulate primed CD4 T cells through OX40 and CD30 at sites where T cells collaborate with B cells. Immunity 18, 643-654
45. Kim MY, Toellner KM, White A et al (2006) Neonatal and adult CD4+ CD3- cells share similar gene expression profile, and neonatal cells up-regulate OX40 ligand in response to TL1A (TNFSF15). J Immunol 177, 3074-3081
46. Fraser H and Dickinson AG (1970) Pathogenesis of scrapie in the mouse: the role of the spleen. Nature 226, 462-463
47. Kimberlin RH and Walker CA (1980) Pathogenesis of mouse scrapie: evidence for neural spread of infection to the CNS. J Gen Virol 51, 183-187
48. Zhang B, Shen P, Yin X, Dai Y, Ding M and Cui L (2020) Expression and functions of cellular prion proteins in immunocytes. Scand J Immunol 91, e12854
49. Brandner S (2003) CNS pathogenesis of prion diseases. Br Med Bull 66, 131-139
50. Fraser H and Dickinson AG (1978) Studies of the lymphoreticular system in the pathogenesis of scrapie: the role of spleen and thymus. J Comp Pathol 88, 563-573
51. Liu YJ, Grouard G, de Bouteiller O and Banchereau J (1996) Follicular dendritic cells and germinal centers. Int Rev Cytol 166, 139-179
52. Aguzzi A, Kranich J and Krautler NJ (2014) Follicular dendritic cells: origin, phenotype, and function in health and disease. Trends Immunol 35, 105-113
53. Heesters BA, Myers RC and Carroll MC (2014) Follicular dendritic cells: dynamic antigen libraries. Nat Rev Immunol 14, 495-504
54. Fischer MB, Goerg S, Shen L et al (1998) Dependence of germinal center B cells on expression of CD21/CD35 for survival. Science 280, 582-585
55. Gitlin AD, Mayer CT, Oliveira TY et al (2015) HUMORAL IMMUNITY. T cell help controls the speed of the cell

cycle in germinal center B cells. Science 349, 643-646
56. Zotos D, Coquet JM, Zhang Y et al (2010) IL-21 regulates germinal center B cell differentiation and proliferation through a B cell-intrinsic mechanism. J Exp Med 207, 365-378
57. McGovern G, Brown KL, Bruce ME and Jeffrey M (2004) Murine scrapie infection causes an abnormal germinal centre reaction in the spleen. J Comp Pathol 130, 181-194
58. Brown KL, Stewart K, Ritchie DL et al (1999) Scrapie replication in lymphoid tissues depends on prion protein-expressing follicular dendritic cells. Nat Med 5, 1308-1312
59. Raeber AJ, Montrasio F, Hegyi I et al (2001) Studies on prion replication in spleen. Dev Immunol 8, 291-304
60. Prinz M, Heikenwalder M, Junt T et al (2003) Positioning of follicular dendritic cells within the spleen controls prion neuroinvasion. Nature 425, 957-962
61. Prinz M, Montrasio F, Klein MA et al (2002) Lymph nodal prion replication and neuroinvasion in mice devoid of follicular dendritic cells. Proc Natl Acad Sci U S A 99, 919-924
62. Montrasio F, Frigg R, Glatzel M et al (2000) Impaired prion replication in spleens of mice lacking functional follicular dendritic cells. Science 288, 1257-1259
63. Bakkebo MK, Mouillet-Richard S, Espenes A, Goldmann W, Tatzelt J and Tranulis MA (2015) The cellular prion protein: a player in immunological quiescence. Front Immunol 6, 450
64. Manni G, Lewis V, Senesi M et al (2020) The cellular prion protein beyond prion diseases. Swiss Med Wkly 150, w20222
65. Ezpeleta J, Boudet-Devaud F, Pietri M et al (2017) Protective role of cellular prion protein against TNFalpha-mediated inflammation through TACE alpha-secretase. Sci Rep 7, 7671
66. Gadotti VM and Zamponi GW (2011) Cellular prion protein protects from inflammatory and neuropathic pain. Mol Pain 7, 59
67. Shao J, Yin X, Lang Y et al (2023) Cellular prion protein attenuates OGD/R-induced damage by skewing microglia toward an anti-inflammatory state via enhanced and prolonged activation of autophagy. Mol Neurobiol 60, 1297-1316
68. Tsutsui S, Hahn JN, Johnson TA, Ali Z and Jirik FR (2008) Absence of the cellular prion protein exacerbates and prolongs neuroinflammation in experimental autoimmune encephalomyelitis. Am J Pathol 173, 1029-1041
69. Petit CS, Barreau F, Besnier L et al (2012) Requirement of cellular prion protein for intestinal barrier function and mislocalization in patients with inflammatory bowel disease. Gastroenterology 143, 122-132 e115
70. Salvesen O, Reiten MR, Espenes A, Bakkebo MK, Tranulis MA and Ersdal C (2017) LPS-induced systemic inflammation reveals an immunomodulatory role for the prion protein at the blood-brain interface. J Neuroinflammation 14, 106
71. Liu J, Zhao D, Liu C et al (2015) Prion protein participates in the protection of mice from lipopolysaccharide infection by regulating the inflammatory process. J Mol Neurosci 55, 279-287
72. Pan Y, Zhao L, Liang J et al (2006) Cellular prion protein promotes invasion and metastasis of gastric cancer. FASEB J 20, 1886-1888
73. Jiang B, Liu J and Lee MH (2019) Targeting a designer TIMP-1 to the cell surface for effective mt1-mmp inhibition: a potential role for the prion protein in renal carcinoma therapy. Molecules 24, 255
74. Ong SH, Goh KW, Chieng CK and Say YH (2018) Cellular prion protein and gamma-synuclein overexpression in LS 174T colorectal cancer cell drives endothelial proliferation-to-differentiation switch. PeerJ 6, e4506
75. Antonacopoulou AG, Grivas PD, Skarlas L, Kalofonos M, Scopa CD and Kalofonos HP (2008) POLR2F, ATP6V0A1 and PRNP expression in colorectal cancer: new molecules with prognostic significance? Anticancer Res 28, 1221-1227
76. Roucou X, Giannopoulos PN, Zhang Y, Jodoin J, Goodyer CG and LeBlanc A (2005) Cellular prion protein inhibits proapoptotic Bax conformational change in human neurons and in breast carcinoma MCF-7 cells. Cell Death Differ 12, 783-795
77. Meslin F, Hamai A, Gao P et al (2007) Silencing of prion protein sensitizes breast adriamycin-resistant carcinoma cells to TRAIL-mediated cell death. Cancer Res 67, 10910-10919
78. Cha S, Sin MJ, Kim MJ et al (2021) Involvement of cellular prion protein in invasion and metastasis of lung cancer by inducing treg cell development. Biomolecules 11, 285
79. Liang J, Pan Y, Zhang D et al (2007) Cellular prion protein promotes proliferation and G1/S transition of human gastric cancer cells SGC7901 and AGS. FASEB J 21, 2247-2256
80. Yap YH and Say YH (2012) Resistance against tumour necrosis factor alpha apoptosis by the cellular prion protein is cell-specific for oral, colon and kidney cancer cell lines. Cell Biol Int 36, 273-277
81. Yun CW, Yun S, Lee JH et al (2016) Silencing prion protein in HT29 human colorectal cancer cells enhances anticancer response to fucoidan. Anticancer Res 36, 4449-4458
82. Gil M, Kim YK, Kim KE, Kim W, Park CS and Lee KJ (2016) Cellular prion protein regulates invasion and migration of breast cancer cells through MMP-9 activity. Biochem Biophys Res Commun 470, 213-219
83. Boulay A, Masson R, Chenard MP et al (2001) High cancer cell death in syngeneic tumors developed in host mice deficient for the stromelysin-3 matrix metalloproteinase. Cancer Res 61, 2189-2193
84. Wang Q, Qian J, Wang F and Ma Z (2012) Cellular prion protein accelerates colorectal cancer metastasis via the Fyn-SP1-SATB1 axis. Oncol Rep 28, 2029-2034
85. Tanaka A and Sakaguchi S (2017) Regulatory T cells in cancer immunotherapy. Cell Res 27, 109-118
86. Shitara K and Nishikawa H (2018) Regulatory T cells: a potential target in cancer immunotherapy. Ann N Y Acad Sci 1417, 104-115
87. Chen BJ, Zhao JW, Zhang DH, Zheng AH and Wu GQ (2022) Immunotherapy of cancer by targeting regulatory T cells. Int Immunopharmacol 104, 108469