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Roles of prion proteins in mammalian development

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ABSTRACT

Prion protein (PrP) is highly conserved and is expressed in most tissues in a developmental stage-specific manner. Glycosylated cellular prion protein (PrP^C) is found in most cells and subcellular areas as a physiological regulating molecule. On the other hand, the amyloid form of PrP^C, scrapie PrP (PrP^{SC}), causes transmissible pathogenesis in the central nervous system and induces degeneration of the nervous system. Although many amyloids are reversible and critical in determining the fate, differentiation, and physiological functions of cells, thus far, PrP^{SC} originating from PrP^C is not. Although many studies have focused on disorders involving PrP^C and the deletion mammalian models for PrP^C have no severe phenotype, it has been suggested that PrP^C has a role in normal development. It is conserved and expressed from gametes to adult somatic cells. In addition, severe developmental phenotypes appear in PrP null zebrafish embryos and in various mammalian cell model systems. In addition, it has been well established that PrP^C is strongly involved in the stemness and differentiation of embryonic stem cells and progenitors. Thus far, many studies on PrP^C have focused mostly on disease-associated conditions with physiological roles as a complex platform but not on development. The known roles of PrP^C depend on the interacting molecules through its flexible tail and domains. PrP^C interacts with membrane, and various intracellular and extracellular molecules. In addition, PrP^C and amyloid can stimulate signaling pathways differentially. In this review, we summarize the function of prion protein and discuss its role in development.

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Introduction

Developmental competency is defined as the ability to perform successfully to the next developmental stage in response to the systemic and local environment. Prion protein (PrP) serves as a receptor and scaffold for various molecules and its role is not exclusively limited to the nervous system (Svedružić et al. 2024). The roles of PrP can be discerned through the molecules with which it interacts, which are context- and cell-dependent (Kovač and Čurin Šerbec 2022). Interestingly, *Prnp* expression occurs in a stage- and time-specific manner according to cell differentiation. According to previous reports, *Prnp* expression is detected from embryonic day 6.5 in extraembryonic tissue and from Day 13.5 in developing central nervous system cells and nonneural cell populations in mice (Manson et al. 1992; Tremblay et al. 2007). In the cardiac mesoderm, *Prnp* is expressed from embryonic day 7.5 (Hidaka et al. 2010). In this regard, recent studies in my laboratory revealed the expression of *Prnp* in oocytes and early-stage embryos (unpublished).

Interestingly cellular prion protein (PrP^C) is a ubiquitous glycoprotein, present in almost all cell types including gametes, cleaving blastocysts, stem cells, committed cells, and progenitors (Bendheim et al. 1992; Castle and Gill 2017; Gilch and Schätzl 2023; unpublished data from Cheon's Laboratory). PrP^C is encoded by *Prnp* gene on chromosome 20 in humans (chromosome 2 in mice) and is conserved throughout vertebrates, as is the homology of its product protein (Vanderperre et al. 2011; Castle and Gill 2017). The mammalian prion gene family includes shadow of prion protein (*Sprn*) encoding shadoo (SPRN) (chromosome 10 in humans, chromosome 7 in mice), and prion-like protein doppel (*Prnd*) encoding doppel (DPL; directly adjacent to *Prnp* approximately 20 kbp downstream; chromosome 20 in humans, chromosome 2 in mice), and prion locus LncRNA (*Prnt*) encoding PRT (chromosome 20 in humans, not found in mice) (Castle and Gill 2017).

The presumption that *Prnp* is a gene associated with development can be attributed to its known expression

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regulation. The expression of the *Prnp* gene is under the control of cis- and trans-regulation. Nerve growth factor, insulin, insulin-like growth factor, endoplasmic reticulum stress, oxidative stress, heat shock, hypoglycemia, copper, all-trans retinoic acid, and genotoxic stress are known to stimulate *Prnp* expression (Haigh and Brown 2006; Bravard et al. 2015). Conformational chromatin modification is also a regulatory factor (Cabral et al. 2002). Anatomical features of *Prnp* gene include a short GC-rich Sp1 binding sites lacking a TATA box in the upstream of its putative transcription start site (Sakudo et al. 2010). This region contains evolutionarily conserved, putative binding sites for numerous transcription factors, such as activator proteins 1 and 2, forkhead box protein O3, regulatory factor X1, heat shock factor 2, GATA-binding factor 3, and thyrotrophic embryonic factor 2. Intron 1 is considered a required region for tissue-specific expression and for synergism with promoter control not as an enhancer (Haigh and Brown 2006; Xue et al. 2012). PrP^C functions in signal transduction without lethality in knockout (KO) models but not in *Prnp* family gene KO mice (Passet et al. 2012; Mantuano et al. 2023). These findings suggest that the *Prnp* gene is one of the developmental genes.

In humans, PrP^C has 253 amino acids and contains an N-terminal signaling peptide, a proline and glycine-rich octapeptide repeats, a highly conserved central hydrophobic segment, a C-terminal hydrophobic region, and a propeptide, which is removed in mature form (Harris 1999). Mature PrP^C, depicted in Figure 1, contains five octapeptide repeats (1 Non-4 Octa) that bind to Cu^{2+} primarily at the N-terminus, a hydrophobic domain in the middle, and a globular C-terminal domain with three α-helices and a two-stranded antiparallel β-sheet (Riek et al. 1996; Béland and Roucou 2012). PrP^C undergoes various types of posttranslational modifications. The majority of mature PrP^C (208 amino acids; amino acids 23–230 of the precursor) is bound to the plasma membrane via a glycosylphosphatidylinositol (GPI)-anchor which is added at Golgi complex with two main N-linked glycosylation sites (N181IT and N197FT in humans and 180 and 196 in mice). Other forms include membrane spanning forms, carboxy-terminal fragment (C1), etc. (Walmsley et al. 2001; Linsenmeier et al. 2017).

PrP^C is found in various subcellular areas such as the plasma membrane, mitochondria, Golgi complex, and nucleus. In plasma membrane, PrP^C is localized in lipid raft membrane domains enriched in phosphatidylinositols, ceramides, cholesterol, and sphingolipids (such as GM3, GM1, and GD3) through GPI anchor (Alves Conceição et al. 2023). PrP^C forms dimers under native conditions and dimerizes for cellular signaling (Roucou 2014). The internalization of PrP^C is mediated by the binding of other proteins. For example, the binding of stress-inducible phosphoprotein 1 (STI1) to PrP^C induces PrP^C endocytosis through extracellular signal-regulated kinase 1 and 2 (ERK1/2) signaling (Caetano et al. 2008). Interaction with the laminin receptor (LRP/LR) also triggers the internalization of PrP^C (Morel et al. 2005).

To date, many studies have attempted to evaluate the possible roles of PrP^C and its related conformational changes. However, it is generally agreed that the roles of PrP^C in development, including the primary developmental physiological function, are unclear. Recently various models have been employed to study the role of PrP^C during development. The aim of this review is to address the current available knowledge on possible roles in developmental function.

Learning from Prnp modified models

The phenotypes associated with PrP^C null or ectopic activation in mouse models have been summarized in a few reviews (Castle and Gill 2017; Wulf et al. 2017; Kishimoto et al. 2020). *Prnp* knockout-mice, -cattle and -goats develop normally without drastic phenotypes. In contrast, in zebrafish, the knockdown of Prp-1 results in severely defective phenotypes, gastrulation arrest and the phenotypes are partial recovery by mouse *Prnp* mRNA (Málaga-Trillo et al. 2009b; Fleisch et al. 2013). In contrast to *in vivo* studies in mammals, *in vitro* models reveal many types of cellular dysfunction, and it is suspected that PrP^C is involved in normal development.

Most $Prnp^{-/-}$ mouse lines were developed on the basis of 129 strain or 129 crossed forms (Striebel et al. 2013; Nuvolone et al. 2016) and formed systematic genetic confounders (Striebel et al. 2013). Among these models some have shown several defects in behavior and neurons in terms of genetic background dependency (Steele et al. 2006; Wulf et al. 2017; Kishimoto et al. 2020; Passet et al. 2020). The RcmO $Prnp^{-/-}$, Ngsk $Prnp^{-/-}$, Rikn $Prnp^{-/-}$, and Zrich II $Prnp^{-/-}$ models exhibit nervous system deficits while accompanying overexpression of *Prnd*, but the Zurich I $Prnp^{-/-}$, Npu $Prnp^{-/-}$ and Edingb $Prnp^{-/-}$ models do not (Schmitz et al. 2014b; Castle and Gill 2017). Recently, Nuvolone et al. (2016) established a strictly co-isogenic $Prnp^{-/-}$ mouse model with TALEN-mediated genome editing tools without *Prnd* overexpression and attempted to confirm these findings. The Zurich-3 (ZH3) *Prnp*-ablated allele in pure C57BL/6J genetic background mice result in any phenotypes described in non-co-isogenic $Prnp^{-/-}$ mice; however, aged $Prnp^{Zh3/ZH3}$ mice developed chronic demyelinating peripheral neuropathy. Brain

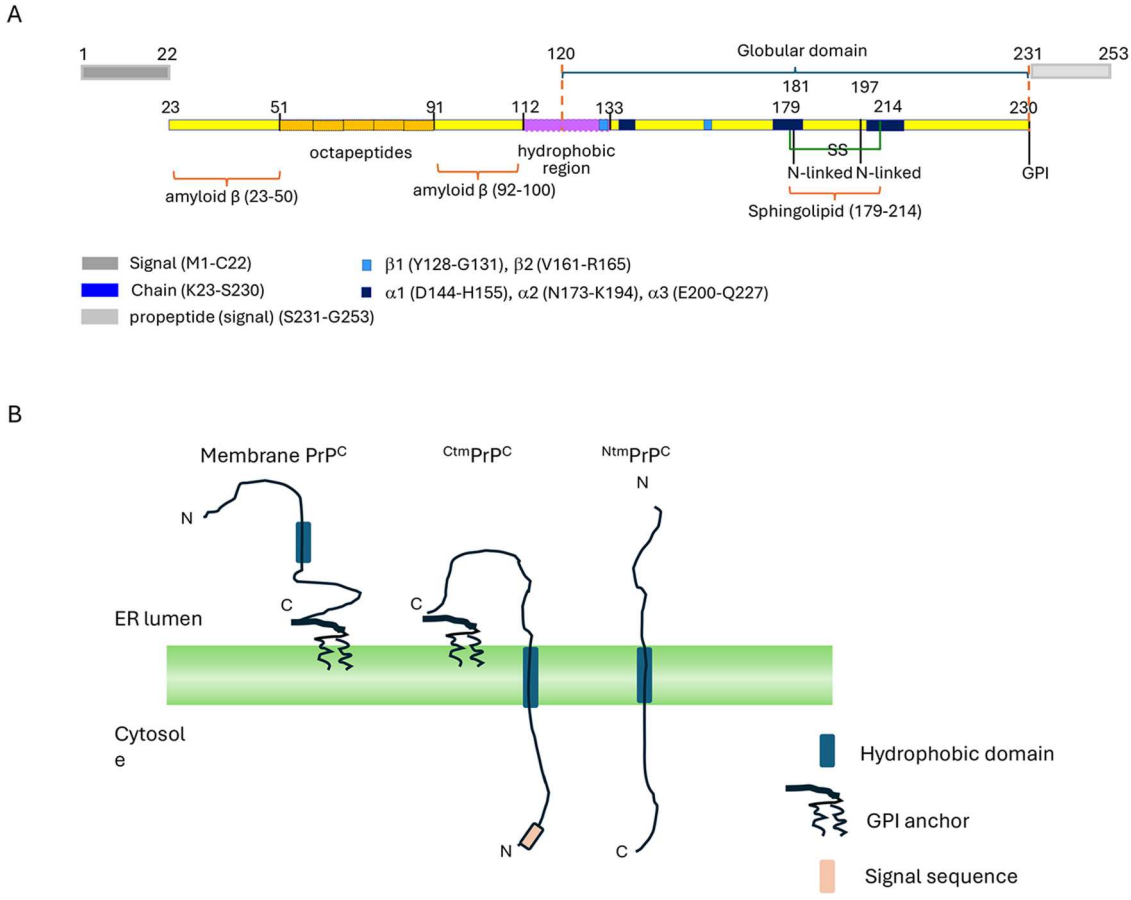

Figure 1. Matured PrP^C and the membrane bound and spanning forms. A, Human prepro-prion protein constituted with 253 amino acids. The N-terminal signaling peptide and C-terminal propeptide region are removed in the mature form. PrP domains contain five octapeptide repeats (1 Non-4 Octa), a hydrophobic domain in the middle, and a globular C-terminal domain with three α-helices and a two-stranded antiparallel β-sheet. B, The forms of membrane PrP^C.

conditional *Prnp* KO postnatal mice are also apparently healthy, with reduced after hyperpolarization potentials in the hippocampal CA1 (cornu Ammonis 1) region (Mallucci et al. 2002). In a mouse model expressing a PrP^C variant with the deletion of amino acids 94-134, a rapidly progressive, lethal phenotype with extensive central and peripheral myelin degradation was observed. Model mice expressing a PrP^C variant with the deletion of amino acids 32–121 and 32–134 die at 3–4 months of age (Shmerling et al. 1998; Radovanovic et al. 2005).

Studies in which the genes regulating PrP^C activity have been manipulated have also been conducted, and phenotypes similar to those of PrP^C KO mice were observed. Post-GPI attachment to protein factor 4 (PGAP4)-KO mice lose the N-acetylgalactosamine (GalNAc) side chain of PrP^C, and both in males and females are fertile, demonstrating that this protein is not essential for embryonic development and fertilization as like other *Prnp* KO mice. However, PGAP4-KO mice exhibit impaired memory and bone formation with grater vulnerability to prion proteins than wild-type mice do (Hirata et al. 2022). Alzheimer's knock-in mice (homozygous $App^{NL\text{-}G\text{-}F}$/hMapt double knock-in mice) lost the synapse in brain, but this loss of synapses is prevented by *Prnp* deletion (Stoner et al. 2023). Recently, in our laboratory, bank vole *Prnp* KI mice were developed, and their fertility of these mice was analyzed. These models yielded results similar to those of other knockout models (unpublished data). In addition, *Prnp*-null goats and cattle have no strict phenotypes, as similar to mouse models (Richt et al. 2007; Zhu et al. 2009). Natural mutants of Norwegian dairy goat with premature stop codon at position 32, exhibit normal reproduction and behavior (Benestad et al. 2012).

As mentioned, the phenotypes of *Prnp* mutant mammals vary according to the genetic models, which may be caused by the redundancies or antagonisms between *Prnp* family proteins with tissue specificity. For example, *Prnp* and *Sprn* double knockout FVB/N mice present the following phenotypes: intrauterine

growth retardation and placental failure with potential redundant or antagonistic roles in different developmental-related pathways (Castille et al. 2021). In an infection study in which Shadoo-specific shRNA expressing lentiviral vectors were used in FVB/N $Prnp^{KO}$ embryos, embryonic lethality was induced with developmental defects in the ectoplacental cone at E7.5 (Passet et al. 2012). Ngsk $Prnp^{0/0}$ mice expressing high levels of *Prnd* exhibit defects in synaptic transmission to Purkinje cells and abnormalities in delayed eyeblink conditioning (Kishimoto et al. 2020). From the various genetic models, we know that PrP^C is needed for the normal development of mammals.

Fate decision and self-renewal

The Cell fate decision is an integral part of development, and during embryo development the cells decide the fate-restricted or not-restricted cells. This decision is regulated by the expression of various genes and physiological regulation mechanisms such as gene transcription, cellular signaling, epigenetic landscapes, protein condensation, and physical stimuli (Guillemin and Stumpf 2021; Wu and Schmitz 2023; Peskett et al. 2024). In cell fate determination and the asymmetric localization of cell fate determinants, cell cycle regulation is required (Prokopenko and Chia 2005). A critical juncture in the G1-phase of the cell cycle, the restriction point, is the point at which the fate decision of a cell, such as proliferation or differentiation, is decided (Dalton and Coverdell 2015; Peskett et al. 2024). In yeast, processing bodies (P-bodies) and the prion-like RNA-binding protein, Whi3, are involved in fate decision (Peskett et al. 2024).

In a few studies, a possible role of PrP^C in the fate decision has been suggested. The stress-inducible protein 1 (SI1)-PrP^C complex enhances the self-renewal of stem cells and progenitor cells in *Prnp* null mice (Santos et al. 2011). The silencing of PrP^C during spontaneous differentiation alters the balance in the lineages of the three germ layers, where differentiation toward the ectodermal lineage fate is suppressed. On the other hand, overexpression in such a condition inhibited the fate of differentiation toward lineages of all three germ layers (Lee and Baskakov 2013). PrP^C expression at bone marrow and lymph organ hematopoietic stem cells associate with the differentiation of these cells (Risitano et al. 2003). Recently a suggested mechanism as fate determining mechanisms is alternative splicing and PrP^C is involved in some gene's alternative splicing. In the case of GSK3β activation regulation, PrP^C down regulate *Taw* exon 10 inclusion (Guillemin and Stumpf 2021).

Interestingly it is revealed that the possible roles of PrP^C in self-renewal capacity of cells. HSCs from *Prnp*-KO bone marrow exhibit impaired self-renewal, which is recovered by introducing *Prnp* expression (Zhang et al. 2006). Prion infection differentially modulates the fate of bone marrow HSCs through autonomous and nonautonomous mechanisms (Sim et al. 2023). In addition, the expression of *Nanog* (a gene involved in self-renewal) is downregulated in *Prnp*-KO ESCs, and the degree of pluripotency is low in embryoid bodies derived from *Prnp*-KO ESCs (Miranda et al. 2011).

PrP^C in cellular community formation and epigenesis

Cellular community formation during development is the step for morphogenesis and it is depending on the ability of communication between cells. One of the unique characteristics of cells is that although they are closed entities, they maintain and control their ability to adapt a condition open to the surrounding environment through their plasma membrane components. Therefore, cells can survive and maintain homeostasis in the environment with harmony along with building an individual. Exogenous signals or stress results in changes in cellular histology/physiology such as shape, enzyme activity, gene expression, and movement to increase their likelihood of survival. During development, inducers induce a specific developmental stage and create new homeostatic conditions. The cellularization and organogenesis stage-specific conditions are formed and chained with the next stage through specific inducers, i.e. exogenous or endogenous signals.

In communication, PrP^C works as a platform. PrP^C platforms play roles in signal transduction processes in a time-dependent manner at the caveolare and lipids of the plasma membrane (Pantera et al. 2009; Sempou et al. 2016; Alves et al. 2020; D'Alessio 2023). For example, PrP^C is involved in the activation of the tyrosine kinase Fyn by forming a complex with caveolin-1 (Pantera et al. 2009). This activation is mediated by Erk1/2 phosphorylation through two distinct signal transduction pathways; 1) reactive oxygen species (ROS) signaling and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase-independent, and 2) Ras-Raf cascade, which is based on interactions with Src family kinases, such as Shc kinase (CsK) (Pantera et al. 2009; Sempou et al. 2016). Growth factor receptor-bound protein-2 (Grb2) can interact with PrP^C, and this complex participates in actin-based cell motility, cell cycle progression, vasculogenesis and angiogenesis, and oncogenesis (Spielhaupter and Schätzl 2001; Soriano et al. 2004). The interaction between β-catenin

and transcription factor 7-like 2 (TCF7L2) and PrP^C upregulates their transcription activity. The interaction between PrP^C and γ-catenin downregulates Wnt pathway activity (Besnier et al. 2015). In addition, PrP^C can be involved in intercellular communication through its cellular transport. Internalized PrP^C is either recycled to the plasma membrane or the Golgi complex or is transported in the pinched-off intraluminal vesicles within multivesicular bodies for exosomes or for degradation in lysosomes (Heisler et al. 2018; Alves et al. 2020). PrP^C forms a complex with muskelin, dynein and KIF5C at transport vesicles (Heisler et al. 2018). The transport vesicles involving exosomes play many depending on their location (Alves et al. 2020).

PrP^C plays a role in the immune system as the activator of immune cells and inflammation, and as the contributor for formation of immune organs such as the spleen and lymph nodes (Kubosaki et al. 2001; Black et al. 2014; Cha and Kim 2023). PrP^C is localized in hematopoietic stem cells, mature lymphoid, and myeloid compartments, such as T and B lymphocytes, natural killer cells, platelets, monocytes, dendritic cells, and follicular dendritic cells (Kubosaki et al. 2001). In human T cells, PrP^C interacts with various molecules, such as F-actin, CD3, Fyn, and mitogen-activated protein kinases (MAPKs) shortly after T cell polyclonal activation (Isaacs et al. 2006). *Prnp* knockdown cause of increased tendency for T-cells to develop a pro-inflammatory phenotype (Hu et al. 2010). In inflammation, PrP^C prevents the NMD receptor-mediated inflammation (Black et al. 2014). The mast cells of humans and mice release PrP^C upon activation by allergic inflammation (Haddon et al. 2009). In complement activation, PrP^C mediates the classical pathway and facilitates complement C4 fixation. Regions encompassing amino acids 90–231 and 121–231 of PrP^C bind complement component 1q (C1q) and activate the classical pathway in a copper-dependent manner (Sjöberg et al. 2008). *Prnp* expression controls the infiltration of immune cells such as mast cells, T effector memory cells, plasmacytoid CD cells, and NK cells in ovarian cancer (Hu et al. 2022).

PrP^C is associated with the homeostasis of some ions and cell structure. PrP^C is involved in Ca^{2+} homeostasis in cells. Plasma membrane-bound PrP^C tunes Ca^{2+} transients in the cytosol and in the mitochondrial matrix and, consequently, Ca^{2+}-associated synaptic plasticity (De Mario et al. 2019). On the other hand, PrP^C is involved in the homeostasis of Cu^{2+} in the cell. Five octapeptide repeats (PHGGGWGQ) in the N-terminus of PrP^C (at around histidines 96 and 111 in human PrP^C) is specific to Cu^{2+} (Faris et al. 2017). Singh et al. (2009) reported that octapeptide-repeat lacking PrP^C mutants show a decreased ferritin iron content. These findings indicate that PrP^C is also involved in cellular iron uptake and transfer to ferritin.

PrP^C protects cells from various toxic stimuli and metabolic challenges. Neurotoxicity in ectopic *Prnd* overexpressing *Prnp*$^{-/-}$ mice can be blocked by PrP^C through physiological protein interactions (Qin et al. 2006). Intracellular PrP^C interacts with BCL2, and blocks the conformational changes of BAX and releases the cytochrome C (Sorice et al. 2012; Faris et al. 2017; Abi Nahed et al. 2023). On the other hand, PrP^C can also be involved in energy balance and metabolism: PrP^C influences glucose homeostasis through PI3K-Akt pathway modulation (Strom et al. 2011; Castle and Gill 2017; Dong et al. 2022; Lu et al. 2022). PrP^C induces lactate production via the transactivation of lactate dehydrogenase A by hypoxia inducible factor 1α and phosphatidylinositide 3-kinase (PI3K)/Akt signaling for survival using glycolysis (Ramljak et al. 2016). PrP^C also involves nuclear acid metabolism through binding to heterogeneous nuclear ribonucleoproteins (hnRNPs) and aldolase (Strom et al. 2006). Regarding metabolism, it has also been suggested that PrP^C plays a regulatory role in the sleep-wake cycle, because the sleep structure is altered in *Prnp*-KO mice (Sánchez-Alavez et al. 2007; Contiliani et al. 2021; Kim et al. 2023a).

Recently, the knowledge for epigenesis dramatically expanded through epigenetics, the study of the mechanisms that are important for the temporal and spatial control of the gene activity required for the development of complex organisms from zygotes to the adults (Holliday 1990) and that are underpinned by alterations in the DNA methylation, histone modifications, noncoding RNAs, and chromatin states involved in normal development as well as disease. Epigenetic mechanisms include DNA/RNA methylation, histone modifications, RNA transcripts, miRNAs, sRNAs, and long non-coding RNAs. By the structural character of prion, prion can be viewed as epigenetic agents capable of inducing a phenotypic change without a modification of the genome. Whether PrP^C is involved in epigenetic regulation has been investigated only a few studies, but the possibility of an epigenetic modulator of PrP^C can be suspected from the karyoplasmic location of PrP^C in the nucleus. PrP^C, which is localized in the nucleus of renewing intestinal epithelium and others acts as a transcriptional cofactor (Besnier et al. 2015; Rousset et al. 2016). At the same time, the possible role of PrP^C as epigenic modulator through histone modifier and chromatin remodeler are suggested (Chakrabortee et al. 2016; Harvey et al. 2020). Harvey et al. (2020) evaluated that Set3C histone deacetylase scaffold Snt1 (NCOR1) drives a prion [ESI+, expressed sub-telomeric information] for expressed sub-telomeric information which is a

mitotically and meiotically stable protein-based epigenetic element. On this basis, a prion epigenetic switch (a stable protein-based epigenetic element) establishes an active chromatin state (Harvey et al. 2020). Recently, it emerged that PrP^C is involved in various diseases such as cancer and Alzheimer's disease, as an epigenetic modulator in invasiveness (Thorne et al. 2012; Rezvani Boroujeni et al. 2020; Ryskalin et al. 2021; Park and Jung 2022; Lee et al. 2023).

Differentiation

Cellular intrinsic factors, ECM organization, and communication through the secreting of signaling molecules and physical cell-to-cell interactions are essential for the differentiation and maintenance of cell functions. The localization and expression profiles of PrP^C suggest that it plays a role in differentiation. The number of cells in a rudiment and tissue is also critical for tissue genesis, organogenesis, and physiological constancy. To date, the roles of PrP^C in differentiation have been studied in a few organs that are associated with prion disease patients. Here we introduced the differentiation in some cells and tissues concerned with it. PrP^C can induce the proliferation and differentiation from pluripotent stem cells into progenitors. PrP^C participates in the transcription of pluripotency markers such as Nanog and Oct4 (Pou5f1) without the compensation effects of PRND and SPRN. Inhibition of PrP^C reduces Nanog expression (Miranda et al. 2011). PrP^C overexpression causes the inhibition of spontaneous differentiation in ESCs, but PrP^C silencing increases spontaneous differentiation by altering the cell cycle and balance in germ cell lineages (Zhang et al. 2006; Miranda et al. 2011; Lee and Baskakov 2013). The expression of PrP^C during embryoid body culture selectively controls the differentiation to neural cells and glial cells (Lee and Baskakov 2014).

In neurogenesis, PrP^C has been extensively studied. During neurulation, PrP^C is expressed spatiotemporally in the central nervous system (CNS) from early to mature stages (Steele et al. 2006; Peralta et al. 2012). PrP^C drives the differentiation of ESCs into neurogenesis including axon guidance, synapse formation, neuroprotection, myelin maintenance and homeostasis, maintenance of ion homeostasis, and signaling (Lee and Baskakov 2014; Küffer et al. 2016). Both the soluble version of PrP^Cs and membrane-anchored PrP^C are involved in these processes. The activation of the AKT/Cdc42/neuronal Wiskott-Aldrich syndrome protein (N-WASP) pathway by the PrP^C-EGFR complex (Martellucci et al. 2018), and the activation of MAPK by PrP^C-STI1 (Lopes et al. 2005) are involved in neuritogenesis. In neuronal polarization Fyn kinase activation by PrP^C (aa 144-154)-NCAM through the regulation of integrin β1 function, fibronectin cell interactions, and cytoskeleton dynamics is essential. During neurite outgrowth, PrP^C-flotillin regulates the trafficking of cargo to the growth cone, the N-terminal domain of PrP^C modulates the activation of mGluR1 (Matsubara et al. 2020), the PrP^C N-terminus (aa23-50 and 51-91) interacts directly with microtubules and Tau for tubulin oligomerization (Osiecka et al. 2011), and residue 105–119 of PrP^C bind to vitronectin (Hajj et al. 2007). During axonal growth, the interaction between basement PrP^C and laminin is also needed and is mediated by the Ras-Raf pathway signaling cascade, activation of phospholipase C, Ca^{2+} mobilization from intracellular stores, and activation of protein kinase C and ERK1/2 (Beraldo et al. 2011; Machado et al. 2012). In addition, PrP^C is involved in myelination. The binding of the N-terminal polybasic cluster of PrP^C to Adgrg6 on Schwann cells elicits the activation of Adgrg6 signals (increase cAMP levels), activates the transcription factor Egr2, and facilitates the maintenance of myelin (Küffer et al. 2016). Ablation of PrP^C causes chronic demyelinating polyneuropathy, and PrP^C can prevent chronic demyelinating polyneuropathy and promote myelin homeostasis through flexible tail-mediated Gpr126 agonism (Henzi et al. 2020).

During synaptogenesis, PrP^C regulates synapse development, the modulation of neurotransmitter release, the formation of neuronal terminals, and neuronal plasticity through interactions with other molecules, such as synapsin-1b and the prion protein interacting protein PRNPIP (ERT1 exonuclease 3) (Spielhaupter and Schätzl 2001; Kim et al. 2023b). In addition, interactions with transcriptional repressor element 1-silencing transcription factor (REST) and synaptic glutamate-gated ion channels, NMDARs, and the γ1C terminal domain of laminin are also known mechanisms (Beraldo et al. 2011; Song et al. 2018). The physical interaction of PrP^C with α2δ-1 of voltage-gated Ca^{2+} channels increases anterograde trafficking and proper synaptic localization and function of the VGCC complex (Senatore et al. 2012). PrP^C rescues defects in synaptic plasticity in hippocampal slices of oligomeric amyloid-beta slices. In long-term memory, a single serotonin pulse is sufficient to generate a mark at the synapse that can then capture prion proteins involved in memory (Martin et al. 1997). The role of PrP^C has also been extended to neuron physiology. PrP^C interacts with NMDARs and reduces overexcitation in neurons (Fan et al. 2016). PrP^C interaction with stress-inducible phosphoprotein 1 (STI1) induces neuroprotective signals and rescues cells from apoptosis (Zanata et al. 2002).

The possible roles of PrP^C in differentiation have also been explained in other cell types. In lymphocytes and

monocytes, PrP^C expression levels downregulated upon differentiation along the granulocyte lineage (Dodelet and Cashman 1998). *In vitro* retinoic acid-induced differentiation of the premyeloid line HL-60 into granulocyte-like cells mimics the suppression of PrP^C in granulocyte differentiation (Dodelet and Cashman 1998). In dendritic cells, the expression of PrP^C increases upon maturation, in parallel with Ag presentation to T cells (Martínez del Hoyo et al. 2006). In addition, PrP^C is required to form the splenic white pulp and for the development of normal levels of CD4T cells and LTi cells; for example, in Zurich I *Prnp*$^{-/-}$ mice, T zone structure is impaired (Kim et al. 2016).

At embryonic day 8 in mice, the PrP^C is localized to cardiac cells (Hidaka et al. 2010). Atypically-shaped cardiomyocytes (ACMs) expressing PrP^C are differentiated into beating ACMs (~500 beating) or into larger multinuclear beating ACMs upon specific culture conditions (Omatsu-Kanbe et al. 2022). On the other hand, the maintenance of PrP^C homeostasis is important for myoblast differentiation. Tao et al. (2023) reported that PrP^C is highly expressed under pathological conditions and that its selective binding to autophagy-related miRNAs, including miR-214-3p inhibits muscle cell differentiation through the inhibition of autophagy-related protein 5-dependent autophagy.

Progenitor cells and tissues

Proliferation is a precondition for differentiation to organogenesis or functional maintenance. PrP^C is involved in cell proliferation. Nuclear PrP^C increases in proliferating enterocytes through interactions with β-catenin and TCF7L2 from the Wnt pathway, which is necessary for proliferation, and PrP^C siRNA inhibits cell proliferation (Besnier et al. 2015). In the subventricular zone, the number of proliferating cells increases by overexpression of PrP^C (Steele et al. 2006). PrP^C can regulate the self-renewal and differentiation of stem cells during development, depending on developmental times, which are involved in homeostasis in tissue and stem cell populations (Martin-Lannerée et al. 2017; Ryskalin et al. 2019). In mesenchymal stem cells (MSCs), PrP^C enhances MSC proliferation and self-renewal. *Prnp* knockdown causes a significant decrease in proliferation, but the retention of PrP^C expression helps to extend the lifespan up to 10 population doublings and increases in engraftment levels along with the increase in superoxide dismutase-2 levels (Mohanty et al. 2012).

In neuroepithelial stem cells, PrP^C maintains homeostasis and development through the control of notch signaling. In the 1C11 neuroepithelial cell line or *in vivo* models, *Prnp* knockdown increases the proportion of ciliated cells and affects the Hedgehog pathway which is important in neurogenesis. PrP^C silencing affects the expression of Jagged 1 and Jagged 2 and Notch receptors while decreasing the expression of EGFR, a Notch target gene in adult neural stem cells (Aguirre et al. 2010; Martin-Lannerée et al. 2017). The interaction of PrP^C with glial fibrillary acidic protein (GFAP) plays a role in the formation of physical barriers to separate damaged tissue from the healthy tissue and in the regulation of the blood–brain barrier to develop a physical barrier to separate damaged tissue and regulating the blood–brain barrier (Miranzadeh Mahabadi and Taghibiglou, 2020).

In intestine, PrP^C plays a key role in intestinal homeostasis by renewing epithelia. PrP^C is necessary for the subcellular distribution of proteins involved in cell architecture. In PrP^C-KO mice, there is a net decrease in the size of desmosomal junctions and a shortening of the length of intestinal villi without changes in cell proliferation. PrP^C involves a balance between proliferation and differentiation (Morel et al. 2008). PrP^C-Src is involved in radiation-induced acute intestinal toxicity, and PrP^C deficiency improves intestinal wound healing (Strup-Perrot et al. 2016). The presence of PrP^C-NCAM1 at the plasma membrane and PrP^C-STI1 at the endoplasmic reticulum support the putative function of PrP^C in morphogenesis in the human pancreas (Hiller et al. 2021; Koyama et al. 2022). In the heart, PrP^C acts as an early adaptive cellular response to a toxic environment, such as oxidative stress conditions, through $p66^{Shc}$ expression and catalase activity. PrP^C is a surface marker of atypically-shaped cardiomyocytes (ACMs), and ACMS is important for tissue homeostasis (Omatsu-Kanbe et al. 2022).

Regulation of cell adhesion

Adhesion between cells is crucial in the development of embryos and morphogenesis (Sisto et al. 2022). The subcellular localization and molecular structure of PrP^C suggest that PrP^C is involved in cell adhesion. Decreased PrP^C expression causes decreased E-cadherin recruitment to the surface and cell migration in glioblastoma stem cells (Solis et al. 2012; Iglesia et al. 2017). Local accumulation of PrP^C at cell contact sites is coupled with the cellular signaling pathways such as the Src-related kinase pathway, along with the recruitment of reggie/flotillin microdomains, and the reorganization of the actin cytoskeleton (Málaga-Trillo and Sempou 2009a, 2009b; Solis et al. 2012). In zebrafish, a prion protein gene PrP-1 knockdown leads to a lethal because the recruitment of E-cadherin to cell contact sites depends on PrP^C-PrP^C transinteraction and ensurs signal transduction (Málaga-Trillo et al. 2009b; Solis et al. 2012).

PrP^C interacts with junctional proteins such as desmosomal proteins (desmoglein-2, plakoglobin, desmoplakin, desmoyokin, etc), adhesion junction proteins (platelet endothelial cell adhesion molecule-1), and tight junction proteins (zonular occludens-1) (Petit et al. 2012; Megra et al. 2018). *Prnp*-KO or *Prnp* knockdown mice are more sensitive to the induction of colitis, with increased paracellular permeability and reduced transepithelial electrical resistance. In these model mice, the levels of E-cadherin, desmoplakin, plakoglobin, claudin-4, occludin, zonula occludens-1, and tricellulin are decreased at cell contacts (Petit et al. 2012; Megra et al. 2018; Ling et al. 2022). For example, in intestinal epithelium-specific PrP^C knockdown mice, paracellular permeability is increased, and barrier function is impaired (Petit et al. 2012; Sarnataro et al. 2016). On the other hand, PrP^C is involved in cell adhesion to the ECM. PrP^C binds to various extracellular matrix molecules, such as sulfated glycosaminoglycans (Pan et al. 2002), neuronal cell adhesion molecule (e.i., N-CAM) (Schmitt-Ulms et al. 2001), neuropilin (West et al. 2005), 37/67kDa nonintegrin laminin receptor (RPSA) (Hundt et al. 2001), stress-inducible protein-1 (Zanata et al. 2002), laminin (Graner et al. 2000), vitronectin (Hajj et al. 2007), and heparan sulfate proteoglycans (Hundt et al. 2001; Hajj et al. 2007).

In addition, it has been suggested that PrP^C serves a role in cell structure either as a regulator or as an interacting molecule (Schmitz et al. 2014a, 2014b). PrP^C is binding to the molecules which are involved in cytoskeletons, microtubule, intermediate filament, and microfilaments (Li et al. 2009; Schmitz et al. 2014a, 2014b).

Therefore, PrP^C can regulate cell adhesion dynamics. For example, PrP^C is involved in adhesion between T lymphocytes and dendritic cells (Ballerini et al. 2006). PrP^C also colocalizes with NCAMs on the surface of polarized NK cells (Mehrabian et al. 2016). PrP^C and PrP^{SC} have high affinity to RPSA. RPSA is one of the major components of basement membranes and has been identified as a nonintegrin cell surface receptor for laminin-1, PrP^C, and PrP^{SC}. The 53–93 aa region of PrP^C serves as an indirect heparan sulfate proteoglycans (HSPG)-dependent interacting domain, and the 144–179 aa region serves as a direct interaction domains (Limone et al. 2023). The silencing of PrP^C in glioblastoma stem-like cells causes a decrease in the expression of CD133, E-cadherin and integrin α6 (Iglesia et al. 2017).

Regeneration

In the field of regeneration, the possible roles of PrP^C have been investigated in only a few studies. However, it is suspected that PrP^C has many roles in regeneration because it is related to stem cells and their proliferation and differentiation. During the regeneration process of adult muscle tissue, the levels of PrP^C do not affect the morphology but the delayed the regeneration. In a study of PrP^C null mice models, it is revealed that PrP^C has roles in regeneration of adult muscle tissue through controlling myogenic precursor cells. The absence of PrP^C significantly slowed regeneration of the hind-limb tibialis anterior muscles by attenuating p38 pathway activity (Stella et al. 2010; Fan et al. 2018). PrP^C is thought to be involved in dental regeneration. PrP^C null mice exhibit earlier formation of mesenchymal derived dentin and epithelial derived enamel (Zhang et al. 2011). PrP^C in proliferating intestinal epithelial cells upregulates the transcriptional activity of the β-catenin/TCF7L2 complex. Silencing PrP^C results in the modulation of the expression of Wnt target genes in crypt cells (Besnier et al. 2015). Experiments have revealed that PrP^C is required for intestinal organoid formation. Interestingly, PrP^C is upstream of β-catenin expression in intestinal cancers, such as colorectal cancer (Mouillet-Richard et al. 2024).

Cancerogenesis

Cancerogenesis is one of the interesting topics in developmental biology because it resembles normal development in critical processes. Increasing evidence has demonstrated that PrP^C acts in tumorigenesis (Corsaro et al. 2016; Abi Nahed et al. 2023; Limone et al. 2023). In solid cancer cells, the role of PrP^C has been studied for proliferation. For example, in a gastric cancer cell line, PrP^C induces cell proliferation through its octapeptide repeat region in a cell type-specific manner (Limone et al. 2023). Ectopically expressed PrP^C promotes cell proliferation through activation of the PI3K/Akt pathway in the human gastric cancer cells SGC7901 and AGS through inducing cyclin D1 expression levels and promoting the G0/G1 to S transition (Liang et al. 2007). Interaction between PrP^C and secreted heat-shock protein 70 (Hsp70)-Hsp90-organizing protein triggers trophic effects in glioblastomas via the PI3K and extracellular-signal-regulated kinase pathways (Lopes et al. 2015). Nevertheless, in some cases, PrP^C has opposite effects as an inhibiting factor. The overexpression of *Prnp* inhibits the proliferation of ovarian cancer cells through the Ras signaling pathway (Hu et al. 2022).

Interestingly, cancer stem cells (CSCs) are highly dependent on PrP^C. *Prnp* down-regulation causes a marked decrease the expression of stemness marker in glioblastoma stem-like cells (GSCs) (Corsaro et al. 2016). Interaction between PrP^C and c-Met enhances cancer stem cell characteristics with higher level

compared to the normal cell. Tumorigenesis associated with PrP^C is accomplished via multiple pathways, including phosphatidyl-inositol-3-kinase (PI3K)-Akt, extracellular signal-regulated kinase (ERK) and Notch (Limone et al. 2023). Silencing PrP^C decreases Notch1 expression and Notch1 signaling in pancreatic ductal adenocarcinoma cells. PrP^C silencing and Notch1 down-regulation inhibit the PI3K/AKT/mTOR pathway to abolish CSC stemness and self-renewal in glioblastoma multiforme (GBM) (Ryskalin et al. 2019). PrP^C is a key factor to enhance the malignant properties of tumors (Limone et al. 2023). The interaction between PrP^C and the laminin receptor (RPSA) regulates tumor development (Limone et al. 2023). In GSCs, *Prnp* knockdown cause of downregulation of cancer stem cell markers, upregulation of cell differentiation markers on the basis of the Hsp70/90 organizing protein (HOP)-PrP^C complex (Iglesia et al. 2017).

In addition, PrP^C is known to play a role in the migration and invasion of tumors. It is known that high levels of PrP^C and/or PrP^C-HOP complex result in enhanced migration and invasion of cancer stem cells (CSCs) (Iglesia et al. 2017). It is revealed that PrP^C promotes epithelial to mesenchymal transition (EMT) via the ERK2 pathway (Du et al. 2013). In colorectal cancer cells, strong expression of PrP^C induces EMT through the modulation of cadherins expression and β-catenin nuclear translocation (Wang et al. 2012). In the human breast cancer cell line MCF7/Adr, the CD44-PrP^C complex binds to EGFR and it causes active invasion and metastasis via the upregulation of cell. The knowledge accumulation in cancerogenesis can be suspected the possible roles in development.

Conclusion

The suggested issues are summarized in Figure 2. PrP^C is localized in various organelles and membranes of various tissues via various post-translational modification and can be transported by secretion and exosomes. Many different developmental and physiological changes have been evaluated in knockout or mutant cells. Studies have shown that antagonistic or compensatory actions occur between prion family members during embryonic stages (Passet et al. 2012;

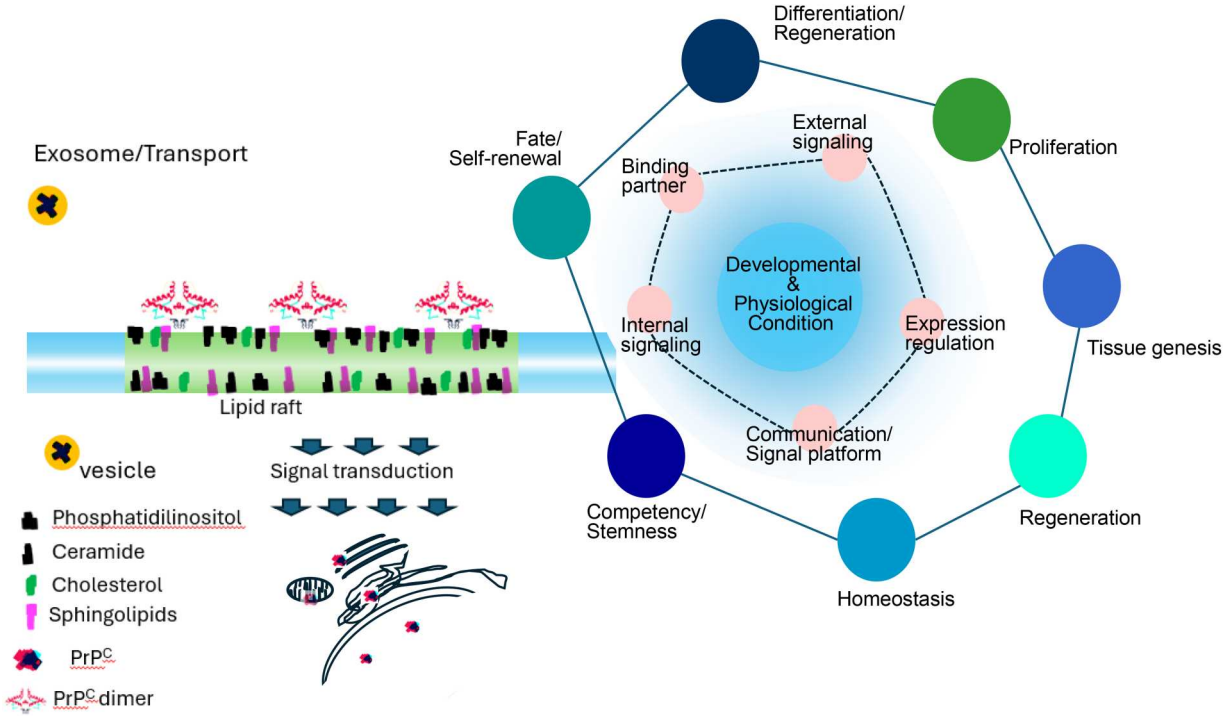

Figure 2. Overview of the possible roles of PrP^C in development. PrP^C is localized in the plasma membrane and other subcellular areas. It works as dimer for signaling, and forms a platform with other proteins in the lipid rafts of the plasma membrane. It also is found in other subcellular areas such as the endoplasmic reticulum and Golgi complexes. It can work at other cells by transporting through as exocrine vesicle or secreted forms. Many researchers have shown the possible roles of PrP^C in the development of mammals from fate decisions to various developmental principal phenomena, including regeneration (solid line). These include internal and external signaling, expression regulation, the formation of signaling platforms, and interactions with various molecules (dashed line). To date, studies on the possible roles of PrP^C in cytoplasm are waiting for much more studies compared to cell membrane-mediated roles. Currently, the possibility of PrP^C in various diseases, such as carcinogenesis and degenerative diseases, is suggested, and it may be concerned with the roles of PrP^C in the development.

2020). To date, much knowledge on the pathophysiological roles of PrP^C has accumulated, but the cure or prevention of prion disease is far from the goal. To cure or prevent diseases such as developmental disorders, cancer, degenerative associate neuronal disease including Alzheimer's disease, and prion disease, it is critical to understand the developmental physiological and developmental roles of PrP^C. In cellular signaling system, PrP^C works as a molecular scaffold protein and its effects are various by the partner molecules. Various methods have been employed to identify the interacting molecules such as isothermal titration calorimetry, circular dichroism spectroscopy, biolayer interferometry, surface plasmon resonance, far-western blotting, complementary hydropathy, flow cytometric analysis of FRET, and computational prediction. However, so far, the interacting molecules are not fully evaluated.

Cellular aggregation has been equated with health issues. Amyloids have a fibrillar morphology, a β-sheet secondary structure and an ordered aggregation (Hong et al. 2023). Amyloids are related to the development of various diseases such as PrP^{SC}. On the other hand, there are also many nonpathological amyloids and termed as functional or physiological amyloid. The role of the latter is to establish a suitable balance between aggregation processes and protein solubilization and refolding (Fassler et al. 2021). It has been suggested that the capacity to form amyloids is an intrinsic property of many proteins (Monsellier et al. 2008). Aggregation is important in different aspects of animal development and linked to development. Therefore, it is interesting to know the profiles of PrP^C expressions and why PrP^C aggregation can cause disease.

Recent studies support the possibility of using PrP^C as a strong mediator for the treatment of cancer, degenerative neural diseases, etc. (Lee et al. 2017; Martellucci et al., 2020). In particular, the molecules than can alter the expression of *Prnp* is a hot issue for that, such as modulators for DNA methyltransferase and histone deacetylases, and anti-PrP^C antibodies (Dexter and Kong 2021; Napper and Schatzl 2023; Mouillet-Richard et al. 2024). The complexity of the roles of PrP^C in developmental physiology and development are beyond description by the interaction with various molecules which are prepared in competent cells. Further studies aimed at understanding the development and stage-specific physiology of PrP^C will provide the future.

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