Review article

Dev Reprod 2024;28(2):29-36
https://doi.org/10.12717/DR.2024.28.2.29

Development & Reproduction

ISSN 2465-9525 (Print)
ISSN 2465-9541 (Online)

Physiology of Cellular Prion Proteins in Reproduction

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Received: March 13, 2024
Revised: March 25, 2024
Accepted: March 30, 2024

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Conflict of interests
The authors declare no potential conflict of interest.

Acknowledgements
This work was supported by National Research Foundation of Korea (NRF)-2021K1A4A7A02098794 and 2023R1A2C3007223121.

Abstract

Cellular prion protein (PrP^C) encoded at *Prnp* gene is well-known to form a misfolded isoform, termed scrapie PrP (PrP^{SC}) that cause transmissible degenerative diseases in central nervous system. The physiological role of PrP^C has been proposed by many studies, showing that PrP^C interacts with various intracellular, membrane, and extracellular molecules including mitochondrial inner membrane as a scaffold. PrP^C is expressed in most cell types including reproductive organs. Numerous studies using PrP^C knockout rodent models found no obvious phenotypic changes, in particular the clear phenotypes in development and reproduction have not demonstrated in these knockout models. However, various roles of PrP^C have been evaluated at the cellular levels. In this review, we summarized the known roles of PrP^C in various cell types and tissues with a special emphasis on those involved in reproduction.

Keywords: Cellular prion protein, Reproduction, Knockout, Scrapie PrP, Scaffold

INTRODUCTION

Cellular prion protein (PrP^C) has been mostly focused by its misfolded, disease-associated scrapie prion protein (PrP^{SC}) that causes transmissible degenerative conditions in the central nervous system known as prion diseases (Gilch & Schatzl, 2023). PrP^{SC} that largely composes the prion pathogen aggregates by themselves and becomes amyloids (Prusiner, 1991). Besides the pathophysiology of PrP^{SC}, the studies to understand the physiological roles of PrP^C are emphasized recently.

PrP^C is a ubiquitous glycoprotein, which is present in almost all cell types (Bendheim et al., 1992; Castle & Gill, 2017; unpublished data in Cheon's Lab). PrP^C is localized in lipid raft membrane domains enriched in phosphatidylinositols, ceramides, cholesterol, and sphingolipids (such as GM3, GM1 and GD3) microdomains through glycosylphosphatidylinositol (GPI) anchor on the extracellular side (Walsh et al., 2014; Mattei et al., 2015). PrP^C is encoded in a *Prnp* gene on chromosome 20 in human and 2 in mouse, and is conserved throughout vertebrates (Vanderperre et al., 2011). It is known that *Prnp* gene is expressed by the result of various stimuli including steroid hormones (Bravard et al., 2015; Peng et al., 2022). Mature PrP^C contains five octapeptide repeats in N-terminal, a hydrophobic domain in the middle, and a globular domain with three α-helices and two stranded antiparallel

Authors' contributions
Conceptualization: Cheon YP, Svedružić ZM.
Writing-original draft: Cheon YP.
Writing-review & editing: Svedružić ZM, Ryou C, Choi D, Lee SH, Cheon YP.

Ethics approval
This article does not require IRB/IACUC approval because there are no human and animal participants.

β -sheets in C-terminal regions (Walmsley et al., 2001; Béland & Roucou, 2012).

PrP^C can work as receptor and scaffold for various molecules and its role is not exclusively limited to the nervous system (Aguzzi et al., 2008). It is suggested that PrP^C forms dimer in native conditions and dimerization may be involved in cellular signaling (Roucou, 2014). The physiological roles of PrP^C can be reasoned through its interacting molecules, and they are context- and cell-dependent (Linden, 2017; Kovač & Čurin Šerbec, 2022). It is revealed that PrP^C can interact with various intracellular and extracellular molecules.

So far, many studies have evaluated the possible roles of PrP^C and its related conformation changes. However, the possible roles of PrP^C are mostly undefined in reproduction, although it is suspected that PrP^C might have many cellular functions. So, in here we review the previous studies and introduce the possible roles of PrP^C in reproduction.

GENERAL FUNCTION OF PRP^C

PrP^C expresses universally from gamete to differentiated cell and interacts with intracellular proteins (Nandi, 1997). Besides, it involves signal transduction through interaction with extracellular proteins and plasma membrane proteins (Hajj et al., 2007). In cell-to-cell communication, PrP^C works as a scaffold. Caveolae, a platform for signal transduction, is the location for PrP^C and it works as a scaffold for signaling modules (Linden, 2017; Martellucci et al., 2020). PrP^C signaling mediation is depending on the binding partners. The known signaling pathways are including follows: Erk1/2 phosphorylation (Isaacs et al., 2006; Caetano et al., 2008), Ras-Raf cascade (Pantera et al., 2009), Wnt-β-catenin cascade (Besnier et al., 2015), Src-related kinase (Málaga-Trillo et al., 2009), etc. On the other hand, PrP^C is also involved in intercellular communication. PrP^C is transported via exosomes and plays many roles according to its localization (Budnik et al. 2016; Sigurdson et al., 2019; Ives et al., 2020). It also works in pathophysiology and becomes a way of prion spread of prion (Sigurdson et al., 2019).

In concerned with histology, PrP^C is involved in cell-to-cell adhesion through trafficking of E-cadherin (Iglesia et al., 2017). PrP^C interacts with junctional proteins such as desmosomal adhesion junctional proteins and tight junctional proteins (Megra et al., 2018). It also interacts with various extracellular matrix molecules including stress-inducible protein-1 and laminin (Hajj et al., 2007). In *Prnp* knockout mice the levels of adhesion molecules are decreased (Petit et al., 2012) and in epithelium-specific *Prnp* knockout mice the paracellular permeability is increased (Sarnataro et al., 2016). On the other hand, PrP^C regulates the cellular structure either as a regulator or as an interacting molecule (Schmitz et al., 2014). The levels of several PrP^C binding cytoskeletal proteins such as intermediary filaments, neurofilament heavy chain, spectrin and vimentin are different in *Prnp* knockout mice (Schmitz et al., 2014). Suppression of PrP^C in pancreatic ductal adenocarcinoma cell line alters the cytoskeleton (Li et al., 2009).

In cellular physiology, ion homeostasis such as Ca^{2+} and Cu^{2+} is regulated by PrP^C (Castle & Gill, 2017). Plasma membrane bound PrP^C tunes Ca^{2+} transients in the cytosol and mitochondrial matrix (De Mario et al, 2019). Cu^{2+} homeostasis in mitochondria is regulated by PrP^C through bidirectional trafficking of Ca^{2+} (Faris et al., 2017). In intracellular transport, PrP^C is involved through forming a complex with muskelin, dynein and IF5C at transport vesicle (Heisler et al., 2018). It also suggested that PrP^C may be involved in energy balance, metabolism, and gene expression. PrP^C promotes glucose uptake through glucose transporter 1 mediated by Fyn-hypoxia-inducible factor-2 α pathway (Li et al., 2011). It also has been known that PrP^C involves in nucleic acid metabolism (Strom et al., 2006), controlling in gene expression through miRNA (Gibbings et al., 2012), and working as histone modifiers and chromatin remodeler (Chakrabortee et al., 2016).

https://doi.org/10.12717/DR.2024.28.2.29

PrP^C is also involved in survivability and immunity in tissues. For example, interactions of PrP^C with ER mitochondria-associated membrane and microtubule network release the cytochrome c (Sorice et al., 2012; Faris et al., 2017). On the other hand, it's well known role is protection of the cells from various toxic stimuli and death (Abi Nahed et al., 2023). Intracellular PrP^C interacts with BCL2 and blocks the conformational changes of BAX (Abi Nahed et al., 2023). In the immune system, PrP^C is a player in immunological quiescence (Bakkebø et al., 2015). In *Prnp* knockout mice, the expression level of IL-10 is less than wild type (Liu et al., 2015).

Recently, it emerged that PrP^C is involved in various disease such as cancer and Alzheimer's disease. The high level of PrP^C drives the proliferation in cancer cells and growth the xenografted tumor via PI3/AKT signaling pathway and cyclin D expression in a cancer cell type-dependent manner (Liang et al., 2007; Limone et al., 2023). PrP^C interacts with various Alzheimer's disease-related proteins such as amyloid-β oligomers (AβO) which accumulation is cause of an early toxic event (Dohler et al., 2014).

REPRODUCTION

During development the expression of *Prnp* is detected from early stage embryos to matured organs as a well conserved gene. The function of PrP^C is suspected to be compensated by its family gene products and not indispensable one. However, the possible roles of PrP^C have been revealed from the study of cell levels. The possible roles of PrP^C in reproductive cells have been summarized through some review papers (Miranda et al., 2013). PrP^C expresses in the reproductive tracts and gonads such as ovary, testis, oviduct, uterine endometrium, myometrium, maternal-/fetal-placenta, follicle, and granulosa cells in mammals including bovine and ovine (Tuo et al., 2001; Thumdee et al., 2007).

Interestingly, it seems like that the *Prnp* is not essential in gametogenesis because the knockout male and female mice are fertile without showing histological changes. Moreover, *Prnp* polymorpism does not affect on reproduction (Gruszecki et al., 2012), although *Prnp* expression is detected in gonad. Recently, we have developed a few genetically modified mice line that express either a transpene or a knock-in (KI) construct of *Prnp* gene. Interestingly, these model mice also showed normal reproduction with the same litter size in both male and female (unpublished data in Cheon's Lab). In fact, previous studies showed that the expression patterns of *Prnp* are dependent on the species. In male mice gonads, *Prnp* expression is restricted to spermatogonia, spermatocytes, round spermatids, and Sertoli cells. 2.2 kb *Prnp* transcript is present in testis at all ages, and 1.1 kb transcript in testis of mice older than two weeks (Fujisawa et al., 2004). The complete and truncated (C- or N-terminally) PrP^C are secreted by the epididymal epithelium (Gatti et al., 2002) and are present in hydrophobic membrane vesicle, epididymosomes and in soluble form in epididymal fluid of the ram (Ecroyd et al., 2004). Functional PrP^C is localized in the sperm membrane raft domains (Ecroyd et al., 2004), suggesting a possibility of a protective role to stress for copper toxicity (Shaked et al., 1999). Consistently, the superoxide dismutase and catalase activity is decreased and suggest the antioxidant function in the whole organism (Klamt et al., 2001). On the other hand, it is suggested that the high expression level of *Prnp* in Sertoli cells supports the development of spermatogonial stem cells (Johnston et al., 2008).

In female reproduction, one of the possible roles of PrP^C is the maintenance of dominance of the selected dominant follicle during folliculogenesis. The levels of *Prnp* are higher in the theca cell of the dominant follicles compared to other stages of follicles but not in granulosa cells (Forde et al., 2008). In mRNA level, the expression of *Prnp* is detected in oocyte in cattle and sheep (Thumdee et al., 2007). In our study, the expression of *Prnp* is detected in oocyte and early stage embryos (Cheon'

Lab unpublished data).

In uterus, it is suggested that PrP^C play a certain role during implantation and decidualization. The *Prnp* expression is detected in spatiotemporal manner during early pregnancy. PrP^C is highly localized in decidual zone at the implantation window stage responding to the embryo implantation (Ding et al., 2018). E2 stimulation up-regulates PrP^C expression in endometrial stromal cells and PrP^C promotes the proliferative, migratory and invasive abilities of endometrial stromal cells. PrP^C promotes cholesterol accumulation and activates estrogen biosynthesis of endometrial stromal cells in a PPAR α pathway-dependent manner (Peng et al., 2022). E2 treatment of ovariectomized (OVX) ewes increases the expression of *Prnp* mRNA and protein in uterus. PrP^C is localized at the stromal cells of deep intercaruncular areas of nonpregnant uterus (Johnson et al., 2014). In placenta, *Prnp* mRNA is localized to a subpopulation of decidual cells (Tanji et al., 1995). PrP^C is immunolocalized in the flattened luminal epithelial cells apposed to the fetal membranes (Johnson et al., 2014).

Although *Prnp* null mice are fertile, the *Prnp* family genes show an effect on fertility. *Prnd* and *Prnt* is considered as a testis-specific protein. *Prnd* gene, aa homolog of *Prnp*, is located near the *Prnp* and its product Doppel (Dpl) has a high homolog with *Prnp* product PrP^C in biochemistry and structure. Dpl expresses in Sertoli cells and at the late stages of spermatogenesis. Dpl-deficient male mice are sterile with the decreased number of spermatids and defection in sperm-egg interaction (129/ola genetic background) (Behrens et al., 2002; Allais-Bonnet & Pailhoux, 2014) or the altered chromatin structure and DNA damage in the sperm (C57BL6/CBA genetic background) (Paisley et al., 2004). However, Dpl null female mice is fertile (Allais-Bonnet & Pailhoux, 2014). On the other hand, in human, *Prnt*, another *Prnp* homolog, is expressed in adult testis, suggesting the role in sperm freezability (Makrinou et al., 2002; Pereira et al., 2018).

CONCLUSION

PrP^C is localized in cellular organelles and membrane of numerous type of tissues (including reproductive organs, embryo, and solid tumors), and it can be transported by secretion and exosome. So far, the phenotypes are not strict in reproduction in knockout and mutant mice of *Prnp* gene. However, many different physiological changes have been evaluated in knockout or mutant cells. Recent studies show the antagonistic or compensation actions between prion family Various molecules are identified as a binding molecule of PrP^C and the possible roles of PrP^C depend on its partners. In male and female, the gametogenesis is not affected by the PrP^C and sperm and egg have normal competence and fertilization ability and forming a normal offspring. Although the further studies to understand the possible roles of PrP^C in reproduction will be provided in the future, so far, the *Prnp* products are not essential by its own existence in mammals, but its family gene products are.

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