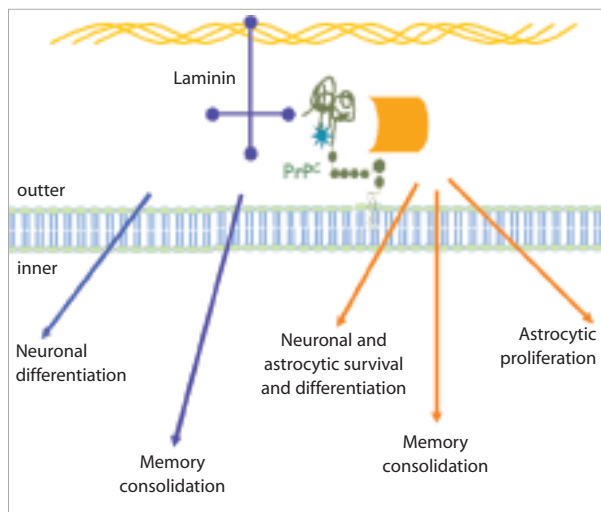


THE ROLE OF CELLULAR PRION PROTEIN IN PHYSIOLOGICAL AND PATHOLOGICAL PROCESSES

Vilma Regina MARTINS

Ludwig Institute for Cancer Research (ILPC)



The Transmissible spongiform encephalopathies (TSE) or prion diseases are a group of fatal neurodegenerative disorders that affects both animals and humans and can exhibit sporadic, inherited or infectious presentations.

The propagation of the disease requires the expression of a GPI (glycosyl-phosphatidylinositol)-anchored cell surface sialoglycoprotein, the cellular prion protein (PrP^C). This protein is converted into an abnormal form, called PrP^{Sc}, through a major conformational change. According to the protein-only hypothesis, the transmission of these diseases does not require nucleic acids, and PrP^{Sc} itself is the infectious prion pathogen.

Most research in the prion field is directed at understanding the nature of the infectious agent, and the mechanistic and structural aspects of the PrP^C conversion to PrP^{Sc} in either infectious or mutation-related pathologies. Nonetheless, the diagnostic procedures available for prion diseases are less sensitive than required and therapeutic interventions for these devastating diseases are still elusive. Furthermore, the risks related to iatrogenic contamination are significant, inclusive the use of blood components, because possible infection by blood transfusion has been recently described in two cases in UK.

The accumulation of the toxic insoluble PrP^{Sc} has been taken as the most probable event responsible for neuronal death in prion diseases. However, since clinical manifestations may occur either before or without characteristic PrP^{Sc} deposits, it has been suggested that neurotoxicity is unlikely to be the unique factor in the pathogenesis of such diseases.

In the last few years several biological functions of PrP^C have been uncovered. The expression of PrP^C is ubiquitous and its interaction with cellular partners mediates cellular survival, differentiation and proliferation. This large spectrum of PrP^C cellular functions indicates that PrP^C loss-of-function could be associated with the pathology of prion diseases but additionally, that alterations in PrP^C activity may also be related to other pathological processes.

SUMMARY OF RESULTS TO DATE AND PERSPECTIVES

Strong evidence for a neuroprotective PrP^C function derives from our description of a putative PrP^C p66 ligand, which was later identified as the Stress Inducible protein 1, STI-1. The interaction between PrP^C and STI-1 prevented programmed cell death and induced neuronal differentiation using cAMP-dependent protein kinase (PKA) and ERK1/2 signaling pathways, respectively. PrP^C also engages to vitronectin which promotes axonal growth in dorsal root ganglia (DRG) neurons. Important clues of PrP^C functional properties were also provided by our observation that PrP^C is a cell surface ligand for laminin and mediates neuronal differentiation.

The normal functions of PrP^C-LN or PrP^C-STI1 were approached *in vivo* and we showed that the association between these molecules induces memory formation and consolidation. These results are particularly relevant for the loss-of-function hypothesis since cognition impairment is one of the initial signals of prion diseases.

PrP^C functions in astrocytes were also addressed and it was demonstrated that PrP^C-STI1 engagement inhibits astrocyte proliferation. Remarkably, astrocytes are able to secrete STI1 which works as a trophic factor for neurons and as an autocrine factor for astrocytes. In human glioblastoma cell lines, contrary to its effect in astrocytes, STI1 promotes PrP^C-dependent proliferation. These data point to an opposite role of PrP^C in normal versus tumoral cells, making PrP^C an interesting therapeutic target to control tumor growth.

All together, our discoveries point for diverse and important physiological functions of PrP^C and support the hypothesis that PrP^C loss-of-function can participate not only in some of the pathological signals of prion diseases but also in other human diseases such as cancer.

MAIN PUBLICATIONS

- Martins VR, Garcia-Abreu J, Souza SJ, et al. 1997. Complementary Hydropathy identifies a cellular prion receptor. *Nature Medicine*. **12**: 1376-1382.
- Graner E, Mercadante AF, Martins VR, Forlenza OV, Cabral ALB, et al. 2000. Cellular prion protein binds laminin and mediates neuritogenesis. *Molecular Brain Research*. **76**: 85-92.
- Chiarini LB, Freitas ARO, Zanata SM, Brentani RR, Martins VR, Linden R. 2002. Cellular prion protein transduces neuroprotective signals. *EMBO Journal*. **21**: 3317-3326.
- Zanata SM, Lopes MH, Mercadante AF, Hajj GNM, Chiarini LB, et al. 2002. Stress Inducible Protein 1 is a cell surface ligand for cellular prion that triggers neuroprotection. *EMBO Journal*. **21**: 3307-3316.
- Lopes MH, Hajj GNM, Muras AG, Mancini GL, et al. 2005. Interaction of cellular prion and stress-inducible protein 1 promotes neurogenesis and neuroprotection by distinct signaling pathways. *Journal of Neuroscience*. **25**: 11330-11339.
- Coitinho AS, Freitas ARO, Lopes MH, Hajj GNM, et al. 2006. The interaction between prion protein and laminin modulates memory consolidation. *European Journal of Neuroscience*. **24(11)**:3255-64.
- Coitinho AS, Lopes MH, Hajj GN, Rossato JI, et al. 2007. Short-term memory formation and long-term memory consolidation are enhanced by cellular prion association to stress-inducible protein 1. *Neurobiology of Disease*. **26(1)**:282-90.
- Hajj GN, Lopes MH, Mercadante AF, Veiga SS, et al. 2007. Cellular prion protein interaction with vitronectin supports axonal growth and is compensated by integrins. *Journal of Cell Science*. **120(Pt 11)**: 1915-1926.
- Lima FRS, Arantes CP, Muras AG, Nomizo R, Brentani RR, Martins VR. 2007. Cellular prion expression in astrocytes modulates neuronal survival and differentiation. *Journal of Neurochemistry*. **103(6)**:2164-2176.
- Erllich RB, Kahn S, Lima FRS, Muras AG, Martins RAP, Linden R, Chiarini LB, Martins VR, Moura Neto V. 2007. STI1 promotes glioma proliferation through MAPK and PI3K pathways. *Glia*. **55**:1690-1698.

Vilma Regina MARTINS

Instituto Ludwig de Pesquisa sobre o Câncer (ILPC)
Rua João Julião, 245, 1º andar – Paraíso
CEP 01323-930 – São Paulo, SP – Brasil
+55-11-3549-0461
vmartins@ludwig.org.br