Available online at www.sciencedirect.com
ScienceDirect
Veterinary Microbiology 123 (2007) 387–393
veterinary microbiology
www.elsevier.com/locate/vetmic

Therapeutic approaches targeting the prion receptor LRP/LR

Chantal Zuber, Heike Ludewigs, Stefan Weiss *

Laboratorium für Molekulare Biologie-Genzentrum, Institut für Biochemie der Ludwig-Maximilians-Universität München, Munich, Germany

Abstract

Transmissible spongiform encephalopathies known as prion diseases are a group of fatal neurodegenerative disorders that affect both humans and animals. The generally accepted principle of the disease is that the conversion of the cellular prion protein (PrP^c) into the disease associated isoform PrP^{Sc} leads to spongiform degeneration of the brain and amyloid plaque formation. Until now no therapy leading to potential alleviation or even cure of the disease exists. It is therefore important to develop therapeutic approaches for the treatment of TSEs since these infections are inevitably fatal and, especially in the case of vCJD, they affect youngsters. Besides current conventional therapeutic strategies, this review summarizes new therapeutic tools targeting the prion receptor LRP/LR.
© 2007 Elsevier B.V. All rights reserved.

Keywords: Bovine spongiform encephalopathy; 37 kDa/67 kDa laminin receptor; LRP/LR; Prion; PrP; Transmissible spongiform encephalopathy; Therapy

1. Introduction

Prion diseases or TSEs are neurological disorders associated with the aggregation of a pathologic isoform of a host-encoded prion protein (PrP). Conversion of the cellular prion protein (PrP^c) into the disease-associated form PrP^{Sc} leads to conformational changes resulting in aggregation and accumulation. Deposition of this abnormal protein takes place mainly in the brain and the lymphoreticular system, accompanied with neuronal vacuolation (spongiosis) and neuronal death. After extremely long incubation times, affected individuals show progressive neurological symptoms terminating in death. Conventional therapeutic approaches use anti-prion compounds which can prolong incubation times but do not lead to a cure. It has been demonstrated that prion propagation *in vitro* requires the laminin receptor (Leucht et al., 2003) implicating that approaches downregulating LRP/LR are a promising alternative strategy for the treatment of prion diseases.

2. Prion diseases in humans and animals

Prion diseases involve rapid neurological decline, accompanied by neuronal loss and spongiform changes caused by accumulation of the aggregated and misfolded prion protein. The most common type

* Corresponding author. Tel.: +49 89 2180 76887; fax: +49 89 2180 76999.
E-mail address: weiss@lmb.uni-muenchen.de (S. Weiss).

0378-1135/$ – see front matter © 2007 Elsevier B.V. All rights reserved.
doi:10.1016/j.vetmic.2007.04.005

of human prion diseases, termed Creutzfeldt-Jakob disease (CJD), can be classified into four categories: sporadic (sCJD), inherited/familial (fCJD), iatrogenic (iCJD) and variant (vCJD). Whereas it has been suggested that the latter results from ingestion/consumption of BSE-contaminated food (Bruce et al., 1997), familial disorders (fCJD) are the inheritance of autosomal-dominant mutations within the *Prn*-p locus. Transplantation of tissues or injection of hormones originating from individuals suffering from CJD or the use of contaminated surgical instruments resulted in the iatrogenic form of CJD. Gerstmann–Sträussler–Scheinker syndrome (GSS), fatal familial insomnia (FFI), its sporadic form (sFI) and kuru are other human prion diseases.

Animal TSEs have been observed in different species: Bovine spongiform encephalopathy (BSE) in cattle, scrapie in sheep and goat, chronic wasting disease (CWD) in cervids such as deer, elk or captive mule and feline spongiform encephalopathy (FSE) in cats or transmissible mink encephalopathy (TME). In addition, some exotic diseases were observed including exotic ungulate encephalopathy (EUE) and primate spongiform encephalopathy (PSE). Transmission of BSE to pigs has been experimentally proven (Wells et al., 2003). Recently, new forms of TSEs with unusual characteristics e.g. an atypical scrapie case (Nor98) (Benestad et al., 2003) have been discovered. Apart from the existing species barrier, the different modes of transmission are not yet understood.

3. Prions and different forms of prion proteins

The term prion was defined by Stanley Prusiner as a ‘‘small proteinaceous particle that resists inactivation by procedures which modify nucleic acids’’, suggesting that a new agent exists beside the commonly known pathogenic organisms such as bacteria, virus or fungi (Prusiner, 1982). The infectious ‘‘agent’’, the prion, and the exact infectious mechanism for prion disorders is just as little understood as the mechanism by which they kill neurons.

PrP^{c} is an ubiquitous membrane-bound glycoprotein attached to the cell surface by a glycosylphosphatidylinositol (GPI) anchor, expressed in many tissues and cell types. Its conversion leads to the disease-associated form PrP^{Sc}, which exhibits a higher β-sheet content correlating with a high tendency to form aggregates. PrP^{Sc} is characterized as insoluble and partially resistant to proteases (Cohen and Prusiner, 1998). Digestion of PrP^{c} with protease K results in the truncated form PrPres (a 27–30 kDa fragment) demonstrating insolubility in aqueous and organic solvents as well as in non-ionic detergents. Additionally, it is completely resistant to proteases. PrP^{Sc} and PrP27-30 both have the tendency to form amyloid fibrils.

4. The 37 kDa/67 kDa LRP/LR as the receptor for PrP^{c}

In a yeast two-hybrid screen we identified the 37 kDa laminin receptor precursor (LRP) as an interaction partner for the prion protein (Rieger et al., 1997). Further *in vitro* studies on neuronal and non-neuronal cells proved that both the 37 kDa LRP and the 67 kDa high affinity laminin receptor function as the receptor for the cellular prion protein (Gauczynski et al., 2001). Direct and indirect heparan sulphate proteoglycane (HSPG)-dependent binding domains on LRP/LR and on PrP have been identified suggesting that HSPGs act as co-factors or co-receptors for PrP^{c} (Hundt et al., 2001). It has been suggested that the 37 kDa LRP is the precursor of the 67 kDa form which was first isolated 1983 from melanoma cells due to its high binding capacity to laminin (Rao et al., 1983). The relationship between the 37 kDa precursor form and the mature 67 kDa isoform is still unknown. Regarding the function of LRP/LR, the 37 kDa LRP appears to be a multifunctional protein involved in the translational machinery (Auth and Brawerman, 1992) and has also been identified as a ribosome-associated protein termed p40 (Makrides et al., 1988). LRP has also been localized in the nucleus, where it is closely associated with nuclear structures (Sato et al., 1996) and binds to DNA through connections with histones H2A, H2B and H4 (Kinoshita et al., 1998). The 37 kDa/67 kDa LRP/LR has been described as a receptor for laminin, elastin and carbohydrates (Ardini et al., 1998), as well as a receptor for Venezuelan equine encephalitis virus (VEE) (Ludwig et al., 1996), Sindbis virus (Wang et al., 1992), Dengue virus (Tio et al., 2005) and Adeno-Associated Viruses (Akache et al., 2006). In addition, studies have been carried out

in order to detect the isoforms that are present in the central nervous system and that bind PrP. Several maturation states of the receptor were identified, including a 44 kDa, 60 kDa, 67 kDa and a 220 kDa form. All of these isoforms were able to bind PrP, suggesting a physiological role for the laminin receptor/PrP interaction in the brain (Simoneau et al., 2003). Although LRP consists of a transmembrane domain (amino acid residue 86–101 (Castronovo et al., 1991)) it is abundant in the cytoplasm (Romanov et al., 1994). In mammalian cells both the 37 kDa LRP and the 67 kDa LR are present in plasma membrane fractions (Gauczynski et al., 2001).

5. The role of LRP/LR in PrP^{Sc} propagation

LRP/LR not only acts as a receptor for the cellular prion protein but also for the infectious PrP27-30, an N-terminal truncated version of PrP^{Sc} (Gauczynski et al., 2006). The importance of LRP/LR in PrP^{Sc} propagation was verified using a polyclonal anti-LRP/LR antibody termed W3 which was able to block and prevent the binding of PrP^{Sc} and to cure scrapie-infected neuroblastoma cells (ScN2a) from PrP^{Sc} (Leucht et al., 2003).

LRP/LR-dependent binding of PrP^{c} and PrP^{Sc} to the cell surface (either alone or together with other co-factors) is accompanied by internalisation which is thought to occur in clathrin-coated pits. After this receptor-mediated endocytosis the conversion of PrP^{c} molecules into the disease-associated form probably takes place in endosomes, lysosomes or endolysosomes. Heparan sulphates also play an essential role in prion uptake and cell infection (Horonchik et al., 2005) suggesting that both the LRP/LR and heparan sulphates act presumably in synergy for PrP^{Sc} binding and internalisation.

The fact that LRP/LR is present in higher amounts in several organs and tissues of scrapie-infected mice and hamsters suggests a correlation between LRP/LR levels and PrP^{Sc} propagation (Rieger et al., 1997). Furthermore, expression studies revealed distribution of the laminin receptor in the intestinal epithelial/brush border confirming that the prion protein uptake and therefore the infection is mediated and supported by this receptor (Shmakov et al., 2000). After oral exposure, TSE agents accumulate in lymphoid tissue, spleen, lymph nodes, tonsils, appendices and Peyer's patches. For this reason prion particles have to cross the intestinal epithelial barrier. Besides the proposition that M-cells are responsible for the uptake of prions (Heppner et al., 2001) has also been suggested that enterocytes are involved in this process, due to the fact that bovine prions are rapidly endocytosed in the presence of LRP/LR (Morel et al., 2005). By preincubating the human enterocytes with the polyclonal anti-LRP/LR antibody, endocytosis of PrP^{BSE} was reduced.

Distribution studies in adult rats revealed that the 67 kDa LR form is highly present in brain regions, classically associated with prion-related neurodegeneration, whereas the 37 kDa form was detected in a subclass of interneurons known to be particularly sensitive to abnormal prion accumulation and cell death during the early stages of CJD (Baloui et al., 2004).

6. Conventional therapeutic strategies for the treatment of TSEs

In recent years, various studies gave evidence that substantial neuropathological changes (e.g. nerve cell degeneration) already occur prior to the onset of symptoms and might be related to PrP^{Sc} accumulation. Accordingly, any effective intervention must aim to start directly after inoculation. Unfortunately, no diagnostic tests are available to detect the disease prior to the onset of symptoms, except for individuals carrying pathogenic mutations within the *Prn*-p gene. Inhibition of PrP^{Sc} formation is the most studied target and can be achieved through (i) inhibition of PrP^{c} synthesis or prevention of its transport to the cell surface, (ii) stabilization of the PrP^{c} structure to make its conformational change unfavourable, (iii) destruction of PrP^{Sc} aggregates, (iv) reversion of PrP^{Sc} to a protease-sensitive form and (v) inhibition of the prion protein receptor(s).

A series of compounds efficiently interfere with PrP^{Sc} accumulation, such as Congo red (Ingrosso et al., 1995) and analogs (Demaimay et al., 1997), certain cyclic tetrapyrrols (Priola et al., 2000) and sulphated polyanions. Although many other compounds have been identified, only flupirtine, an analgetic, had beneficial effects on cognitive function

for human CJD patients (Otto et al., 2004). The anthracycline 4′-iodo-4′-deoxy-doxorubicin (IDX) was able to delay clinical signs of the disease and prolong the survival time in scrapie-infected hamsters (Tagliavini et al., 1997). It was also shown that quinacrine reduces the protease resistance of PrP peptide aggregates and is able to inhibit the *in vitro* conversion of the normal prion protein (PrP^c) to the abnormal form (PrPres) (Barret et al., 2003). Chlorpromazine was reported to increase incubation time in mice after intracerebral, but not intraperitoneal, injection (Roikhel et al., 1984), but was less effective in cell culture than quinacrine (Korth et al., 2001). Unfortunately, most substances that inhibit PrP^{Sc} formation show only significant effects when administered long before the clinical onset of the disease. Since no effective therapy for clinically affected TSE patients is available these diseases are inevitably fatal.

PrP-specific antibodies, a promising alternative tool in TSE treatment, counteract prion propagation both *in vitro* (Enari et al., 2001; Peretz et al., 2001; Perrier et al., 2004) and *in vivo* (Buchholz et al., 2006). In a murine model, treatment with a monoclonal anti-PrP antibody delayed the development of prion disease (White et al., 2003). Application of monoclonal antibodies raised against recombinant PrP also resulted in a reduction of PrP^{Sc} levels in infected mouse neuroblastoma cells (Pankiewicz et al., 2006). Paracrine secretion of single chain antibodies (scFv) directed against PrP^c revealed an anti-prion effect in neuroblastoma cells (Donofrio et al., 2005).

7. Therapeutic approaches targeting LRP/LR

7.1. Trans-dominant negative LRP mutants

Recently, it has been shown that an LRP mutant encompassing the extracellular domain of LRP/LR (LRP102-295::FLAG) might act in a trans-dominant negative way as a decoy by trapping PrP molecules (Fig. 1, I) (Vana and Weiss, 2006). *In vitro* studies revealed that the LRP mutant is able to reduce the

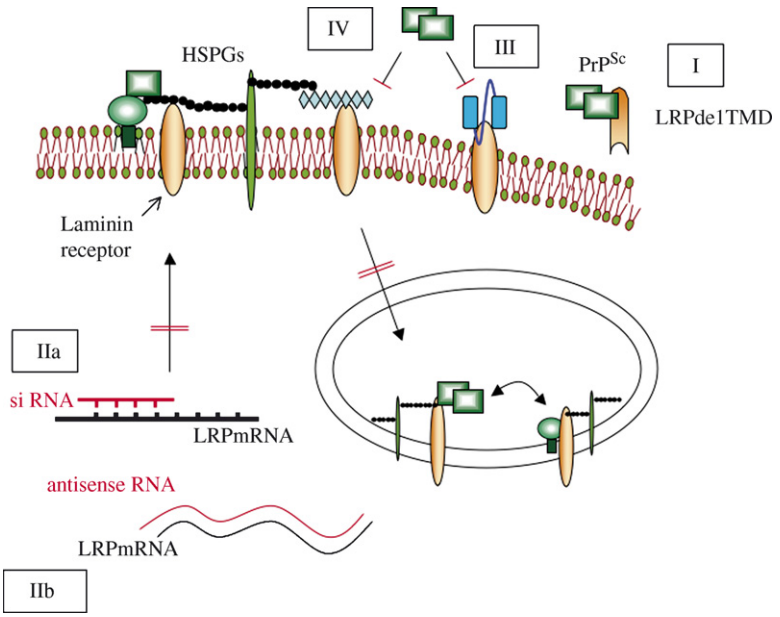

Fig. 1. Molecules inhibiting the PrP-LRP interaction and reducing the LRP/LR levels. LRP/LR (orange) is able to bind both the cellular prion protein (green circle) and the infectious PrP^{Sc} (green rectangle). After binding to the LRP/LR–HSPG complex the prion protein becomes internalized into endo-/lysosomal compartments where the conversion of PrP^c to PrP^{Sc} might take place. Prevention of the binding to LRP/LR is achieved by (I) trapping PrP^{Sc} by a LRP mutant (delTMD) encompassing the extracellular domain (LRP102-295), downregulation of LRP/LR by (IIa) siRNAs and (IIb) antisense RNA directed against LRP mRNA, (III) anti-LRP/LR antibodies (blue rectangles) competing with PrP for LRP binding sites and (IV) heparan mimetics interfering with the binding of PrP^{Sc} to the LRP/LR/HSPG complex.

PrP^{Sc} formation in scrapie-infected neuronal cells (Vana and Weiss, 2006) and might therefore represent a promising novel tool in TSE therapy.

7.2. RNA interference and antisense RNA

A further strategy used to influence the PrP^{Sc} propagation level is the knockdown of LRP/LR by siRNA and antisense RNA technology. This has already successfully been shown for PrP using *Prn*-p-specific sequences. Thus, the transfection of siRNAs corresponding to the murine *Prn*-p triggered specific *Prn*-p-gene silencing in scrapie-infected neuroblastoma cells. This caused a rapid loss of their PrPres content (Daude et al., 2003). Accordingly, it was shown that transfection of either LRP antisense RNA or LRP-specific siRNAs in scrapie-infected neuronal cells results in downregulation of LRP/LR expression and prevention of PrP^{Sc} propagation (Fig. 1, II) (Leucht et al., 2003).

Furthermore, a permanent effect of knockdown of disease-relevant genes using RNAi has been achieved using a lentivirus-mediated gene transfer (Ralph et al., 2005; Raoul et al., 2005). Recently it was shown that lentivector-mediated RNAi efficiently suppressed the prion protein and prolonged survival of scrapie infected mice (Pfeifer et al., 2006). This suggests that an alternative lentivirus-based RNAi gene therapy approach using HIV-derived vectors expressing LRP-specific siRNAs might represent another promising approach in TSE treatment.

7.3. Antibodies directed against the LRP/LR

The PrP binding capacity of LRP offers strategies in therapeutic approaches against prion diseases. The curative effect of the polyclonal anti-LRP/LR antibody (W3) on scrapie infected N2a cells recommends anti-LRP antibodies as therapeutic tools for the treatment of prion diseases (Leucht et al., 2003). On the molecular level this antibody (i) prevents the binding of infectious prions to mammalian cells (Fig. 1, III) (Gauczynski et al., 2006) and (ii) blocks endocytosis of PrP^{BSE} by enterocytes mediated by the LRP/LR is inhibited after treatment with W3 (Morel et al., 2005). Moreover W3 was able to prolong the incubation/survival time in scrapie mice (Zuber et al., submitted).

Since a polyclonal antibody format is not suitable for a therapy in animals or humans the development of single-chain antibodies directed against LRP/LR provides a promising alternative therapeutic strategy. Smaller (30 kDa) and with better tissue penetration, they can be delivered via passive immunotransfer for example intracerebrally into the brain region where massive prion propagation takes place. So far, no immune response or side reactions have been observed after application of scFvs. In a murine scrapie model passively delivered anti-LRP/LR single chain antibodies reduced peripheral prion propagation (Zuber et al., in press). To circumvent the problem of the short half-life in organisms a permanent delivery of single chain antibodies directed against LRP/LR may be achieved by gene therapeutic strategies employing AAV-based or lentiviral vector systems.

7.4. Polysulphated glycans

Polysulphated glycans such as heparan mimetics (HM) or pentosan polysulphate interfere with the binding of the infectious PrP27-30 to the LRP/LR–HSPG complex and are therefore alternative promising therapeutic tools (Fig. 1, IV) (Gauczynski et al., 2006). Treatment of scrapie-infected mice with pentosan polysulphate resulted in a prolonged incubation time and even in the cure of two mouse strains infected with two different scrapie strains (Farquhar and Dickinson, 1986). Moreover, it has been shown that GAGs (Hijazi et al., 2005), especially heparan sulphate, (Horonchik et al., 2005) also act as receptors for the infectious PrP^{Sc}. Polysulphated glycans such as SP54 and PS3 (phycarin sulphate) also show an inhibitory effect on the binding of PrP27-30 to LRP hyperexpressing BHK cells (Gauczynski et al., 2006). Both pentosan polysulphates and heparan sulphate mimetics are able to prolong the incubation time in rodent models and interfere with PrP^{Sc} propagation in neuronal cells due to the inhibition of the LRP/LR dependent binding of prions to target cells.

8. Conclusions

So far, there is no TSE treatment available that is able to cure affected individuals. Alternative therapeutic strategies targeting LRP/LR might be promising since it

acts as the receptor for PrP^{c} and PrP^{Sc}. Molecules targeting the LRP–PrP interaction such as LRP mutants, LRP/LR-specific antibodies and polysulphated glycans or tools downregulating the LRP/LR levels such as siRNAs and antisense RNAs might be effective in the treatment of prion disorders.

Acknowledgments

We thank the Federal Ministry of Research and Education (grants 01-KO-0106 and KO-01-0514), the Bavarian Prion Research Foundation (grant LMU 4) and the European Commission (grants QLRT-2000-02085 and NoE NeuroPrion FOOD-CT-2004-506579) for financial support.

References

Akache, B., Grimm, D., Pandey, K., Stephen, R.Y., Xu, H., Kay, M.A., 2006. The 37/67-Kilodalton Laminin Receptor is a receptor for Adeno-Associated Virus Serotypes 8,2,3, and 9. J. Virol. 80, 9831–9836.

Ardini, E., Pesole, G., Tagliabue, E., Magnifico, A., Castronovo, V., Sobel, M.E., Colnaghi, M.I., Menard, S., 1998. The 67-kDa laminin receptor originated from a ribosomal protein that acquired a dual function during evolution. Mol. Biol. Evol. 15, 1017–1025.

Auth, D., Brawerman, G., 1992. A 33-kDa polypeptide with homology to the laminin receptor: component of translation machinery. Proc. Natl. Acad. Sci. U.S.A. 89, 4368–4372.

Baloui, H., von Boxberg, Y., Vinh, J., Weiss, S., Rossier, J., Nothias, F., Stettler, O., 2004. Cellular prion protein/laminin receptor: distribution in adult central nervous system and characterization of an isoform associated with a subtype of cortical neurons. Eur. J. Neurosci. 20, 2605–2616.

Barret, A., Tagliavini, F., Forloni, G., Bate, C., Salmona, M., Colombo, L., De Luigi, A., Limido, L., Suardi, S., Rossi, G., Auvre, F., Adjou, K.T., Sales, N., Williams, A., Lasmezas, C., Deslys, J.P., 2003. Evaluation of quinacrine treatment for prion diseases. J. Virol. 77, 8462–8469.

Benestad, S.L., Sarradin, P., Thu, B., Schonheit, J., Tranulis, M.A., Bratberg, B., 2003. Cases of scrapie with unusual features in Norway and designation of a new type, Nor98. Vet. Rec. 153, 202–208.

Bruce, M.E., Will, R.G., Ironside, J.W., McConnell, I., Drummond, D., Suttie, A., McCardle, L., Chree, A., Hope, J., Birkett, C., Cousens, S., Fraser, H., Bostock, C.J., 1997. Transmissions to mice indicate that 'new variant' CJD is caused by the BSE agent. Nature 389, 498–501.

Buchholz, C.J., Bach, P., Nikles, D., Kalinke, U., 2006. Prion protein-specific antibodies for therapeutic intervention of transmissible spongiform encephalopathies. Expert. Opin. Biol. Ther. 6, 293–300.

Castronovo, V., Taraboletti, G., Sobel, M.E., 1991. Functional domains of the 67-kDa laminin receptor precursor. J. Biol. Chem. 266, 20440–20446.

Cohen, F.E., Prusiner, S.B., 1998. Pathologic conformations of prion proteins. Annu. Rev. Biochem. 67, 793–819.

Daude, N., Marella, M., Chabry, J., 2003. Specific inhibition of pathological prion protein accumulation by small interfering RNAs. J. Cell Sci. 116, 2775–2779.

Demaimay, R., Adjou, K.T., Beringue, V., Demart, S., Lasmezas, C.I., Deslys, J.P., Seman, M., Dormont, D., 1997. Late treatment with polyene antibiotics can prolong the survival time of scrapie-infected animals. J. Virol. 71, 9685–9689.

Donofrio, G., Heppner, F.L., Polymenidou, M., Musahl, C., Aguzzi, A., 2005. Paracrine inhibition of prion propagation by anti-PrP single-chain Fv miniantibodies. J. Virol. 79, 8330–8338.

Enari, M., Flechsig, E., Weissmann, C., 2001. Scrapie prion protein accumulation by scrapie-infected neuroblastoma cells abrogated by exposure to a prion protein antibody. Proc. Natl. Acad. Sci. U.S.A. 98, 9259–9299.

Farquhar, C.F., Dickinson, A.G., 1986. Prolongation of scrapie incubation period by an injection of dextran sulphate 500 within the month before or after infection. J. Gen. Virol. 67 (Pt 3), 463–473.

Gauczynski, S., Nikles, D., El-Gogo, S., Papy-Garcia, D., Rey, C., Alban, S., Barritault, D., Lasmezas, C.I., Weiss, S., 2006. The 37-kDa/67-kDa laminin receptor acts as a receptor for infectious prions and is inhibited by polysulfated glycanes. J. Infect. Dis. 194, 702–709.

Gauczynski, S., Peyrin, J.M., Haik, S., Leucht, C., Hundt, C., Rieger, R., Krasemann, S., Deslys, J.P., Dormont, D., Lasmezas, C.I., Weiss, S., 2001. The 37-kDa/67-kDa laminin receptor acts as the cell-surface receptor for the cellular prion protein. EMBO J. 20, 5863–5875.

Heppner, F.L., Christ, A.D., Klein, M.A., Prinz, M., Fried, M., Kraehenbuhl, J.P., Aguzzi, A., 2001. Transepithelial prion transport by M cells. Nat. Med. 7, 976–977.

Hijazi, N., Kariv-Inbal, Z., Gasset, M., Gabizon, R., 2005. PrPSc incorporation to cells requires endogenous glycosaminoglycan expression. J. Biol. Chem. 280, 17057–17061.

Horonchik, L., Tzaban, S., Ben-Zaken, O., Yedidia, Y., Rouvinski, A., Papy-Garcia, D., Barritault, D., Vlodavsky, I., Taraboulos, A., 2005. Heparan sulfate is a cellular receptor for purified infectious prions. J. Biol. Chem. 280, 17062–17067.

Hundt, C., Peyrin, J.M., Haik, S., Gauczynski, S., Leucht, C., Rieger, R., Riley, M.L., Deslys, J.P., Dormont, D., Lasmezas, C.I., Weiss, S., 2001. Identification of interaction domains of the prion protein with its 37-kDa/67-kDa laminin receptor. EMBO J. 20, 5876–5886.

Ingrosso, L., Ladogana, A., Pocchiari, M., 1995. Congo red prolongs the incubation period in scrapie-infected hamsters. J. Virol. 69, 506–508.

Kinoshita, K., Kaneda, Y., Sato, M., Saeki, Y., Wataya-Kaneda, M., Hoffmann, A., 1998. LBP-p40 binds DNA tightly through associations with histones H2A, H2B, and H4. Biochem. Biophys. Res. Commun. 253, 277–282.

Korth, C., May, B.C., Cohen, F.E., Prusiner, S.B., 2001. Acridine and phenothiazine derivatives as pharmacotherapeutics for prion disease. Proc. Natl. Acad. Sci. U.S.A. 98, 9836–9841.

Leucht, C., Simoneau, S., Rey, C., Vana, K., Rieger, R., Lasmezas, C.I., Weiss, S., 2003. The 37 kDa/67 kDa laminin receptor is required for PrP(Sc) propagation in scrapie-infected neuronal cells. EMBO Rep. 4, 290–295.

Ludwig, G.V., Kondig, J.P., Smith, J.F., 1996. A putative receptor for Venezuelan equine encephalitis virus from mosquito cells. J. Virol. 70, 5592–5599.

Makrides, S., Chitpatima, S.T., Bandyopadhyay, R., Brawerman, G., 1988. Nucleotide sequence for a major messenger RNA for a 40 kilodalton polypeptide that is under translational control in mouse tumor cells. Nucleic Acids Res. 16, 2349.

Morel, E., Andrieu, T., Casagrande, F., Gauczynski, S., Weiss, S., Grassi, J., Rousset, M., Dormont, D., Chambaz, J., 2005. Bovine prion is endocytosed by human enterocytes via the 37 kDa/67 kDa laminin receptor. Am. J. Pathol. 167, 1033–1042.

Otto, M., Cepek, L., Ratzka, P., Doehlinger, S., Boekhoff, I., Wiltfang, J., Irle, E., Pergande, G., Ellers-Lenz, B., Windl, O., Kretzschmar, H.A., Poser, S., Prange, H., 2004. Efficacy of flupirtine on cognitive function in patients with CJD: a double-blind study. Neurology 62, 714–718.

Pankiewicz, J., Prelli, F., Sy, M.S., Kascsak, R.J., Kascsak, R.B., Spinner, D.S., Carp, R.I., Meeker, H.C., Sadowski, M., Wisniewski, T., 2006. Clearance and prevention of prion infection in cell culture by anti-PrP antibodies. Eur. J. Neurosci. 23, 2635–2647.

Peretz, D., Williamson, R.A., Kaneko, K., Vergara, J., Leclerc, E., Schmitt-Ulms, G., Mehlhorn, I.R., Legname, G., Wormald, M.R., Rudd, P.M., Dwek, R.A., Burton, D.R., Prusiner, S.B., 2001. Antibodies inhibit prion propagation and clear cell cultures of prion infectivity. Nature 412, 739–743.

Perrier, V., Solassol, J., Crozet, C., Frobert, Y., Mourton-Gilles, C., Grassi, J., Lehmann, S., 2004. Anti-PrP antibodies block PrPSc replication in prion-infected cell cultures by accelerating PrPc degradation. J. Neurochem. 89, 454–463.

Pfeifer, A., Eigenbrod, S., Al-Khadra, S., Hofmann, A., Mitteregger, G., Moser, M., Bertsch, U., Kretzschma, H., 2006. Lentivector-mediated RNAi efficiently suppresses prion protein and prolongs survival of scrapie-infected mice. J. Clin. Invest. 116, 3204–3210.

Priola, S.A., Raines, A., Caughey, W.S., 2000. Porphyrin and phthalocyanine antiscrapie compounds. Science 287, 1503–1506.

Prusiner, S.B., 1982. Novel proteinaceous infectious particles cause scrapie. Science 216, 136–144.

Ralph, G.S., Radcliffe, P.A., Day, D.M., Carthy, J.M., Leroux, M.A., Lee, D.C., Wong, L.F., Bilsland, L.G., Greensmith, L., Kingsman, S.M., Mitrophanous, K.A., Mazarakis, N.D., Azzouz, M., 2005. Silencing mutant SOD1 using RNAi protects against neurodegeneration and extends survival in an ALS model. Nat. Med. 11, 429–433.

Rao, N.C., Barsky, S.H., Terranova, V.P., Liotta, L.A., 1983. Isolation of a tumor cell laminin receptor. Biochem. Biophys. Res. Commun. 111, 804–808.

Raoul, C., Abbas-Terki, T., Bensadoun, J.C., Guillot, S., Haase, G., Szulc, J., Henderson, C.E., Aebischer, P., 2005. Lentiviral-mediated silencing of SOD1 through RNA interference retards disease onset and progression in a mouse model of ALS. Nat. Med. 11, 423–428.

Rieger, R., Edenhofer, F., Lasmezas, C.I., Weiss, S., 1997. The human 37-kDa laminin receptor precursor interacts with the prion protein in eukaryotic cells. Nat. Med. 3, 1383–1388.

Roikhel, V.M., Fokina, G.I., Pogodina, V.V., 1984. Influence of aminasine on experimental scrapie in mice. Acta Virol. 28, 321–324.

Romanov, V., Sobel, M.E., pinto da Silva, P., Menard, S., Castronovo, V., 1994. Cell localization and redistribution of the 67 kD laminin receptor and alpha 6 beta 1 integrin subunits in response to laminin stimulation: an immunogold electron microscopy study. Cell Adhes. Commun. 2, 201–209.

Sato, M., Kinoshita, K., Kaneda, Y., Saeki, Y., Iwamatsu, A., Tanaka, K., 1996. Analysis of nuclear localization of laminin binding protein precursor p40 (LBP/p40). Biochem. Biophys. Res. Commun. 229, 896–901.

Shmakov, A.N., Bode, J., Kilshaw, P.J., Ghosh, S., 2000. Diverse patterns of expression of the 67-kD laminin receptor in human small intestinal mucosa: potential binding sites for prion proteins? J. Pathol. 191, 318–322.

Simoneau, S., Haik, S., Leucht, C., Dormont, D., Deslys, J.P., Weiss, S., Lasmezas, C., 2003. Different isoforms of the non-integrin laminin receptor are present in mouse brain and bind PrP. Biol. Chem. 384, 243–246.

Tagliavini, F., McArthur, R.A., Canciani, B., Giaccone, G., Porro, M., Bugiani, M., Lievens, P.M., Bugiani, O., Peri, E., Dall'Ara, P., Rocchi, M., Poli, G., Forloni, G., Bandiera, T., Varasi, M., Suarato, A., Cassutti, P., Cervini, M.A., Lansen, J., Salmona, M., Post, C., 1997. Effectiveness of anthracycline against experimental prion disease in Syrian hamsters. Science 276, 1119–1122.

Tio, P.H., Jong, W.W., Cardosa, M.J., 2005. Two dimensional VOPBA reveals laminin receptor (LAMR1) interaction with dengue virus serotypes 1, 2 and 3. Virol. J. 2, 25.

Vana, K., Weiss, S., 2006. A trans-dominant negative 37 kDa/67 kDa laminin receptor mutant impairs PrPSc propagation in scrapie-infected neuronal cells. J. Mol. Biol. 358, 57–66.

Wang, K.S., Kuhn, R.J., Strauss, E.G., Ou, S., Strauss, J.H., 1992. High-affinity laminin receptor is a receptor for Sindbis virus in mammalian cells. J. Virol. 66, 4992–5001.

Wells, G.A., Hawkins, S.A., Austin, A.R., Ryder, S.J., Done, S.H., Green, R.B., Dexter, I., Dawson, M., Kimberlin, R.H., 2003. Studies of the transmissibility of the agent of bovine spongiform encephalopathy to pigs. J. Gen. Virol. 84, 1021–1031.

White, A.R., Enever, P., Tayebi, M., Mushens, R., Linehan, J., Brandner, S., Anstee, D., Collinge, J., Hawke, S., 2003. Monoclonal antibodies inhibit prion replication and delay the development of prion disease. Nature 422, 80–83.

Zuber, C., Knackmuss, S., Rey, C., Reusch, U., Röttgen, P., Fröhlich, T., Arnold, G., Mitteregger, G., Pace, C., Kretzschmar, H.A., Little, M., Weiss, S., 2007. Single chain Fv antibodies directed against the 37kDa/67kDa laminin receptor as therapeutic tools in prion diseases. Mol. Imm., in press.