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The GPI-anchoring of PrP
Implications in sorting and pathogenesis

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The cellular prion protein (PrP^C) is an N-glycosylated GPI-anchored protein usually present in lipid rafts with numerous putative functions. When it changes its conformation to a pathological isoform (then referred to as PrP^{Sc}), it is an essential part of the prion, the agent causing fatal and transmissible neurodegenerative prion diseases. There is growing evidence that toxicity and neuronal damage on the one hand and propagation/infectivity on the other hand are two distinct processes of the disease and that the GPI-anchor attachment of PrP^C and PrP^{Sc} plays an important role in protein localization and in neurotoxicity. Here we review how the signal sequence of the GPI-anchor matters in PrP^C localization, how an altered cellular localization of PrP^C or differences in GPI-anchor composition can affect prion infection, and we discuss through which mechanisms changes on the anchorage of PrP^C can modify the disease process.

PrP, a GPI-Anchored Protein

The prion protein (PrP^C) acquires two post-translational modifications along the secretory pathway: the addition of up to two N-glycan moieties at positions 181 and 197 (human amino acid numbering) and a glycosylphosphatidylinositol (GPI)-anchor at position 230 which attaches the protein to the outer leaflet of the plasma membrane (reviewed in ref. 1). Through a yet not fully understood mechanism, PrP^C, which is highly expressed in neurons, can change its conformation into an abnormal protease-resistant, potentially infectious isoform (PrP^{Sc}). The latter is an essential part of the agent responsible for transmissible spongiform encephalopathies (TSE), the prion, and is still GPI-anchored.[2,3] In this review, to simplify matters, we will use the term PrP^{Sc} as a general term for disease-associated PrP species independently of their biochemical properties or aggregation status, although it should be noted that different terms exist that imply conceptual differences.

The GPI-anchorage is highly conserved among eukaryotes and used by 10–20% of all membrane proteins in eukaryotic cells. Biosynthetically it is a complex attachment involving more than 20 genes implicated in ten reactions in the endoplasmatic reticulum (ER) which are not yet fully understood.[4,5] GPI-anchored proteins (GPI-APs) have a wide range of functions ranging from receptors and cell surface hydrolases to adhesion molecules among others[6,7] but there is no clear correlation between GPI-APs and distinct biological functions. Therefore it is hypothesized that the GPI-anchor bestows some advantages over other types of more simple attachments. For instance, GPI-APs are more mobile within the plane of the lipid bilayer and occupy less space than proteins with a transmembrane domain, allowing the proteins to be more tightly packed together. Moreover, GPI-APs also have the capacity of modifying the lipid composition of the membrane itself[8] and GPI-anchors may also be necessary to complete the formation of the functional structure of the protein as described for Thy-1, another GPI-AP highly expressed in neurons.[9,10] One intriguing capacity of GPI-APs is their ability to be spontaneously inserted into membranes in vitro and in vivo, a phenomenon known as "cell surface painting,"[11,12] which has also been observed for PrP^C.[13]

All GPI-APs contain a signal sequence at the N-terminus that directs the protein to the ER during synthesis at the ribosome. Once it is translocated to the ER, a second hydrophobic signal sequence (SS-GPI) present at the C-terminus of the protein is removed by a transamidase in a fast reaction of about a minute and a pre-formed GPI-anchor is attached.[14] All GPI-anchors contain a common structure composed of an ethanolamine phosphate in an amide linkage to the C-terminal carboxyl group of the protein, a highly conserved glycan core of three mannose residues, glucosamine and a phosphatidylinositol (PI) group, and phospholipid tails that attach the GPI-anchor to the cell membrane. The addition of side-branching sugars and modifications of the lipid moiety during the passage through the secretory pathway to the plasma membrane depends on the type of cell and organism, thus leading to a large structural diversity. Of note, PrP^C is one of only three proteins (the others being porcine membrane dipeptidase[15] and CD59[16]) known to date that contain a sialic acid in their GPI-anchor structures[17] (reviewed in ref. 18).

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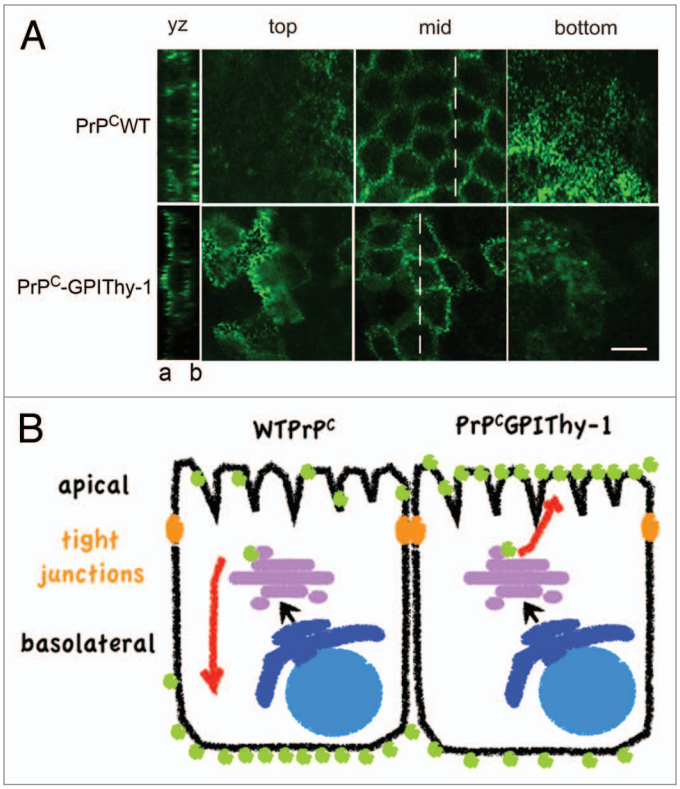

Figure 1. PrP^C and PrP^{C}GPIThy-1 expression in MDCK cells. (**A**) Confocal microscopy showing Z-stacks taken from top to bottom. As published before[33] PrP^C (in green) is basolaterally (b) sorted in fully polarized MDCK cells whereas changing the SS-GPI of PrP^C for the one of Thy-1 preferentially directs the PrP^{C}GPIThy-1 to the apical (a) compartment. Scale bar is 10 μm. Reprinted with permission from PLoS One. (**B**) Schematic representation of the differential sorting of wild type (WT) PrP^C and PrP^{C}GPIThy-1 shown in (**A**).

The Signal Sequence of GPI (SS-GPI) as a Sorting Signal

Interestingly, further lipid remodeling of the GPI-anchor occurs in the Golgi apparatus where the GPI-APs associate to specialized microdomains known as lipid rafts or detergent resistant membranes (DRMs). These domains are described as nanodomains highly enriched in sphingolipids and sterols that contain specific proteins and that can coalesce by lipid-lipid, protein-lipid, and protein-protein interactions[19] forming a platform for signal transduction through cellular receptors.[20-23] In fact, several GPI-APs, which are attached to the outer leaflet of the plasma membrane, can signal through tyrosine kinases after raft clustering,[24] probably mediated by transmembrane proteins that are also found in lipid rafts.[25]

It has been proposed that the GPI-anchor is a sorting signal for selective targeting to lipid rafts and, in the majority of instances, a sorting signal for being apically sorted in polarized cells and to axons in neurons.[26-29] However, some exceptions to this rule have been described and, in fact, PrP^C is one of these exceptions, being sorted mainly basolaterally in Madin-Darby canine kidney cells (MDCK), which represent a well-established model of polarized cells.[30] Concerning signals that direct PrP^C to the basolateral membrane, Paladino et al. proposed that the SS-GPI could play a role in its sorting. Thus, when the green fluorescent protein (GFP) is attached to the SS-GPI of PrP^C, it is sorted basolaterally whereas when it is attached to the SS-GPI of the folate receptor, it is directed to the apical side in MDCK cells. The same authors also suggested that the differential mechanism for apical vs. basolateral sorting of GPI-APs in lipid rafts could be the ability of the apically sorted GPI-APs to form high molecular mass complexes (HMM) in the Golgi apparatus,[31] which could depend on the SS-GPI.[32] As shown in **Figure 1**, our studies also revealed that, when the SS-GPI of PrP^C is replaced by the one of Thy-1, the resulting PrP^{C}GPIThy-1 relocates from the basolateral to the apical side in MDCK cells.[33] PrP^C and Thy-1 both reside in lipid rafts but share different lipid environments within these domains speaking in favor of structurally heterogeneous raft domains[34,35] which could have a role in sorting through HMM formation.[36] The localization of PrP^C in neurons is more controversial. Here it can be found enriched in either axons or cell bodies and dendrites.[35,37,38] How a signal peptide, that is removed in less than a minute after the protein is translocated into the ER, can affect the sorting of GPI-APs and maybe the GPI-anchor structure and/or the lipid environment, is a question that remains unanswered. However, other factors apart from membrane composition can play a role. It is known that the SS-GPI markedly influences the efficiency of the transamidation process, which in turn may influence membrane localization.[11,39] In a more daring concept it has also been proposed that different signal sequences can actually direct the addition of different types of GPI-anchors.[40,41] However, experimental proof of such a mechanism is still required.

It is important to note that three point mutations (M232R, M232T, and P238S) located at the SS-GPI of PrP^C lead to familial prion disease in humans.[42] It has been proposed that the two first mutations are related to an increased transmembrane orientation which could explain neurotoxicity.[43] More recently, Guizzunti et al. used a chimeric protein expressing EGFP with the SS-GPI of PrP linked to a Myc tag to demonstrate that the P238S mutation in the SS-GPI of PrP prevents degradation of the SS-GPI by the proteasome. As a consequence the cleaved SS-GPI peptide tends to accumulate in the ER. With this elegant approach, the authors monitored for the first time the fate of a GPI-anchor signal peptide and also provided an hypothesis of how mutations in the SS-GPI of PrP^C might contribute to the development of prion disease.[44]

The GPI-Anchor of PrP^C and Its Role in Prion Disease

The type of membrane attachment or modifications in the GPI-anchor of PrP^C has an impact in the pathophysiology of prion disease. The site of conversion of PrP^C to PrP^{Sc} has been proposed to be at the plasma membrane and/or in the endocytic compartment[45-47] with the requirement that PrP^C and PrP^{Sc} are attached to the same raft domain at the membrane in cell-free conversion reactions.[48] A recent study using tagged PrP^C, which

is able to be converted to PrP^{Sc}, pinpointed de novo formation of PrP^{Sc} at the plasma membrane to lipid raft-enriched domains. Conspicuously, this is a very fast process taking about a minute. PrP^{Sc} is then rapidly internalized into early endosomes.[49,50] These studies imply that any perturbation of lipid rafts will have an effect on prion conversion. For instance, depletion of cholesterol, either by inhibiting its biosynthesis[51] or by addition of amphotericin B or filipin treatment (antibiotics known to sequester cholesterol), has been shown to decrease or inhibit PrP^{Sc} formation.[52,53] On the other hand, when PrP^{C} is recombinantly expressed as a transmembrane protein ($CD4PrP^{C}$), which is then targeted out of lipid rafts, PrP^{Sc} formation is also abolished.[54] Moreover, although GPI-anchorless PrP^{C} can be efficiently converted to PrP^{Sc} in a cell-free conversion assay,[55] cells expressing GPI-anchorless PrP^{C} do not support persistent infection.[56] Thus, in vitro, the presence of PrP^{C} at the cell surface is a prerequisite for efficient conversion to PrP^{Sc}.[57]

Taken together, these reports indicate that PrP^{C} localization in lipid raft-enriched domains is of high importance for prion conversion. Interestingly, only when the amyloidogenic yeast protein Sup35 is attached to a GPI-anchor, it can be propagated to neighboring cells and these cells can then sustain and propagate the aggregates for many passages. This may raise the idea that prion diseases, in contrast to other protein misfolding diseases such as Alzheimer disease, are naturally transmissible because PrP^{C} is the only amyloidogenic protein carrying a GPI-anchor.[58]

Recent reports highlighted the idea that prion infection can be modified not only by the presence or absence of its GPI-anchor or by disrupting lipid rafts but also by altering the structure/composition of the GPI-anchor itself. Nisbet et al. showed that by exchanging amino acids at the C-terminal moiety within the SS-GPI of murine PrP^{C} (MoPrP) by the ones of rabbit PrP^{C} (RbPrP, rabbits are naturally relatively resistant to prion infection[59]), the resulting MoPrP-RbGPI becomes resistant to PrP^{Sc} conversion.[60]

Interestingly, studies coming from the group of Bate and Williams showed that modifications in the lipid part of the GPI-anchor or of the sialic acid residue lead to alterations in cholesterol at the plasma membrane and to reduced PrP^{Sc} loads and infectivity (these experiments are discussed below in the section "Signaling Through PrP^{C}").

In vivo, the scenario becomes more complex. Neuropathologically, prion diseases are characterized by the presence of diffuse or (more rarely) amyloidic depositions of PrP^{Sc}, neuropil vacuolation (spongiosis) as well as abundant astrogliosis and microglial activation. On the ultrastructural level, many of the lesions that are specific for TSE and co-localize with PrP^{Sc} are related to lesions of the plasma membrane.[61]

Although the presence of PrP^{C} is mandatory in order to develop prion diseases,[62] in inducible knockout mice infected with prions, the pathological changes in the brain are reverted once PrP^{C} production is shut off, in spite of further PrP^{Sc} accumulation.[63] This is very interesting because there is growing evidence that in prion diseases there are two mechanistically different, yet related phenomena, the conversion of PrP^{C} to PrP^{Sc} (prion propagation) and the neurotoxic signaling.[64] The latter is probably dependent on membrane attachment of PrP^{C} via its GPI-anchor and on the localization of PrP^{C} within lipid rafts as discussed later.

To study the issue of GPI-anchor attachment in vivo, Chesebro and colleagues generated mice expressing GPI-anchorless PrP^{C} and infected them with mouse-adapted prions. They showed that GPI-anchorless PrP^{C} is neither present in lipid rafts nor at the plasma membrane but that it is able to be converted to PrP^{Sc}, which presents with abundant thioflavin S-positive PrP^{Sc} amyloid plaques, especially around blood vessels. In these mice, infectivity was preserved but clinical onset of disease was delayed. When the animals died of disease, neurodegeneration was attributed to direct damage by amyloidic PrP^{Sc} accumulation either by disrupting the brain tissue or by causing vascular damage.[65] Interestingly, the mice displayed a conspicuous lack of spongiosis. Spongiotic lesions can occur in a variety of neurodegenerative conditions but the type of vacuoles seen in TSE is very specific and genuine. The vacuole membrane is fragmented and contains membranes and granular osmiophilic granules.[61] These changes are independent of PrP^{Sc} deposition. The lack of spongiotic changes in the GPI-anchorless mice was attributed either to a decreased toxicity of amyloidic anchorless PrP^{Sc} or to the absence of the GPI-anchor and thus to the lack of neurotoxic events. Our own results also point in this direction as we have generated transgenic animals expressing PrP^{C} with the SS-GPI of Thy1 (PrP^{C}GPIThy-1) and we have observed that there is a relocalization of PrP^{C}GPIThy-1 to the axons. Moreover, after prion-infection, there is a delayed onset to clinical disease accompanied by an altered neuropathology, different prion strain characteristics, and decreased amounts of PrP^{Sc} (Puig et al., unpublished results).

Taken all of this into consideration, an important question arises: what are the mechanisms through which the alteration of membrane composition or alterations in the GPI-anchorage lead to changes in prion conversion and neurotoxicity? Regarding prion conversion, for GPI-anchorless PrP^{C} it is clear that conversion is enhanced (as has also been shown in cell culture models[48]) but neurotoxicity is decreased. In other instances, such as in our PrP^{C}GPIThy-1 transgenic mice, when PrP^{C} is localized in another cellular compartment, it is possible that direct interaction between PrP^{C} and PrP^{Sc} is reduced at the plasma membrane and that conversion is thus slowed down. For the conversion of PrP^{C} to PrP^{Sc} a cofactor is considered necessary (reviewed in ref. 66). Many proteins have been proposed to interact with PrP^{C} but in vitro-data suggest that glypican-1, an heparan sulfate proteoglycan (HSPG) resident in lipid rafts, actually acts as a scaffolding protein that keeps PrP^{C} and PrP^{Sc} in lipid rafts and facilitates prion conversion.[67] Therefore, meeting specific partners/cofactors in the appropriate lipid raft domain may be of importance for efficient PrP^{Sc} formation. One can also hypothesize that the endocytic pathway, necessary for the prion replication, is also altered. In fact, the mechanism of internalization of PrP^{C} is different compared with other GPI-anchored proteins, which are usually endocytosed via a clathrin-independent pathway, although this largely depends on the cell type.[68] PrP^{C} leaves raft domains in order to be endocytosed via clathrin-coated pits

and is rapidly endocytosed in primary neurons. Thy-1, in contrast, is internalized with a much slower rate and via non-coated vesicles.[69] The low-density lipoprotein receptor-related protein 1 (LRP1) is thought to be the transmembrane protein that supports PrP^C to be internalized via clathrin-coated pits.[70,71] Other mechanisms implicating cooperation between lipid rafts and clathrin have also been proposed.[72] One might speculate that by changing either the properties of the GPI-anchor or the membrane composition, endocytosis might be altered with regard to rates and routes of internalization.

With regard to toxicity and neurodegeneration, the signaling pathways that are linked to PrP^C could likewise be modified by alterations in the lipid composition of the GPI-anchor as well as by proteolysis of PrP^C. These issues will be briefly discussed in the following sections.

Signaling Through PrP^C

Many reviews are dedicated to the role of signaling through PrP^C in cell adhesion and in neurite extension/maintenance.[73,74] Here we will only focus on how alterations of lipid rafts or changes in the GPI-anchor could lead to disturbances in signaling implicated in prion diseases and, briefly, other proteinopathies.

As pointed out above, in vitro-studies from the group of Bate and Williams show that manipulation of the GPI-anchor composition leads to modulation of prion infection, implicating phospholipase A_2 ($cPLA_2$) as the toxic signaling pathway.[75,76] $cPLA_2$ is involved in the generation of signaling molecules through the arachidonic acid pathway but also in membrane trafficking (reviewed in ref.77). On the one hand, clustering of PrP^C, either mediated through antibodies or by addition of PrP^{Sc}, increases the cholesterol content in membranes and activates $cPLA_2$ signaling, which then triggers synaptic damage. $cPLA_2$ activation and synaptic damage could not be observed after clustering of Thy-1, indicating a specific effect of PrP^C. The authors inferred that it is the clustering of the GPI-anchors, either caused by antibody cross-linking or PrP^{Sc} aggregation, that leads to neurotoxic effects. Importantly, when either the sialic acid or (one or both) acyl-chains are removed from the GPI-anchor of PrP^C, or when the acylation of the GPI-anchor of PrP^{Sc} is altered, these neurotoxic effects are not observed. The authors proposed that the membrane composition is altered in the presence of either monoacylated or desialylated PrP^C and that $cPLA_2$ can consequently not be activated.[78] A similar scenario is observed when PrP^C is administered to prion-infected neuronal cell lines and integrates itself into the outer leaflet of the plasma membrane. This leads to increased amounts of cholesterol content in membranes and increased activation of $cPLA_2$, together with an increased production of PrP^{Sc}. On the contrary, when monoacylated PrP^C (PrP^C-G-lyso-PI) is introduced, these effects are abolished. PrP^C-G-lyso-PI is not present in lipid rafts, is not converted to PrP^{Sc}, and seems to displace $cPLA_2$ from PrP^{Sc}-containing rafts, thus no longer permitting toxic signaling. Moreover, a decrease in PrP^{Sc} production is observed suggesting either that PrP^C-G-lyso-PI is an inefficient template for conversion or that it competes with PrP^C for partners involved in endocytosis, thus altering the trafficking and limiting the interactions between PrP^C and PrP^{Sc}.[79,80]

Other partners for signal transduction via PrP^C have been described. For instance, PrP^C has been involved in the inhibition of excitotoxicity mediated by the N-methyl-D-aspartate receptor (NMDAR).[81] It has been hypothesized that this regulation is executed either through direct interaction of PrP^C with NMDAR subunits (PrP^C co-immunoprecipitates with the NR2D subunit of the NMDAR) or via protein kinases[82] such as the Src tyrosine kinase family member Fyn.[83] Of note, NMDARs localize in lipid raft domains but can also be present in non-raft domains after phosphorylation.[84] Moreover, cholesterol depletion reduces localization of NMDARs in lipid rafts and leads to neuroprotection.[85] On the other hand, Mouillet-Richard et al. first described Fyn as being activated by crosslinking of PrP^C.[86] Since then, this pathway has been implicated in many of the functions that are attributed to PrP^C, for instance its role as a neuronal receptor for toxic amyloid β (Aβ) oligomers.[87] Binding of Aβ oligomers derived from patients with Alzheimer disease activates the Fyn pathway leading to NR2B phosphorylation and altered NMDAR localization.[88-90] However, clustering of PrP^C by crosslinking failed to activate this pathway, suggesting that binding of β-sheet-rich oligomers leads to a conformational change in PrP^C that is necessary to activate this pathway. It has been suggested that the concept of PrP^C as a receptor for toxic oligomers can be generalized for other β-sheet-rich oligomers found in different neurodegenerative conditions (including PrP^{Sc} in prion diseases) and that the toxicity following this interaction is mediated by NMDAR.[91] The same authors highlighted the importance of PrP^C localization in lipid rafts to mediate toxic signaling, since a transmembrane form of PrP (CD4PrP) did not mediate any toxic effects. Other kinases that are altered as a consequence of PrP^{Sc} binding to PrP^C include ERK1/2, JNK, and the CREB transcription factor.[92,93] A schematic draw synthesizing the issues discussed here is shown in **Figure 2**.

Anchorage and Localization of PrP^C May Influence Its Proteolytic Processing

Proteolytic processing reflects an additional aspect of prion protein biology that is likely to be influenced by modifications of the membrane lipid composition or in the GPI-anchor attachment resulting in alterations in PrP^C localization. In recent years it has become increasingly obvious that evolutionary conserved cleavage events, especially the α-cleavage in the center of PrP^C[94] and the shedding in close proximity to its GPI-anchor,[95,96] not only regulate PrP^C membrane homeostasis and reduce amounts of full-length PrP^C and, thus, the mediator of neurotoxic signaling and the substrate for conformational prion conversion. In addition, these cleavages produce biologically active fragments[97,98] (reviewed in ref. 99). Of note, the released soluble fragments, N1 (for α-cleavage) and shed PrP as well as their artificial correlates, have recently been linked with neuroprotection by blocking both the access of toxic oligomeric protein species to the cell as well as the conversion process in the context of prion diseases.[91,100-107] Thus, it is not surprising that these cleavage events are currently

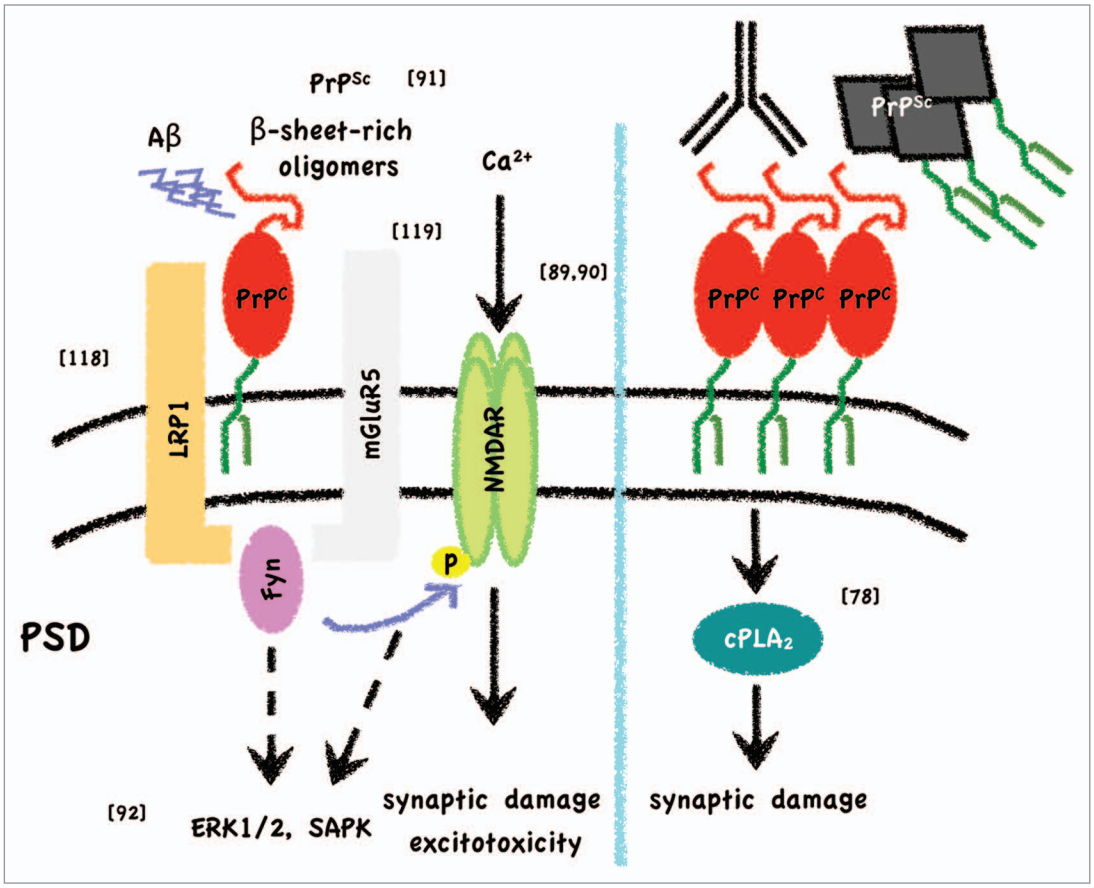

Figure 2. Simplified scheme of toxic signaling through PrP^C. On the one hand (left) it has been described that PrP^C can bind Aβ oligomers at the post-synaptic density (PSD), either derived from recombinant sources or from brains of Alzheimer disease patients, and elicit toxicity through Fyn activation, NMDAR phosphorylation and altered localization.[88,90] Phosphorylation of NMDAR subunits would then lead to dendritic spine loss and excitotoxicty. As long as PrP^C is attached to the outer leaflet of the membrane and Fyn to the inner, it has been proposed that a transmembrane protein should act as a scaffold. LRP1[118] and mGluR5[119] have been suggested as the interacting transmembrane partners after Aβ oligomer binding to PrP^C. Resenberger et al. also showed that this signaling cascade can apply for various β-sheet rich conformers.[91] In the case of PrP^{Sc} binding, apart from Fyn activation, other signaling targets, such as ERK1/2, p38 and JNK, are seen to be activated in neuronal cell lines.[92] In addition, it might be hypothesized that β-sheet rich oligomer-associated NMDAR activation per se induces MAP kinase pathways. On the other hand (right) experiments by Bate and Williams demonstrated that after either crosslinking of PrP^C with antibodies or by applying PrP^{Sc} to cortical primary neurons, there is an increase in membrane cholesterol content that leads to a toxic pathway implicating $cPLA_2$ and arachidonic acid metabolites.[78] Reference to original studies are given by the numbers in brackets.

discussed as therapeutic targets with regard to prion diseases and other neurodegenerative proteinopathies.

The identity of the protease(s) responsible for the α-cleavage remains a matter of controversy (reviewed in refs. 108 and 109) and a recent study suggests a more complex scenario than initially expected, involving different members of the ADAM family of metalloproteases.[110] In contrast, the role of ADAM10 as the major PrP^C sheddase has been established by recent studies.[95,96,107,111]

While knowledge on the concrete localization of the two cleavage events is limited[54,111-113] both processing steps seem to depend on PrP^C membrane attachment. As a matter of implicitness, for a protein to be proteolytically cleaved it has to meet and interact with the relevant protease. Therefore, it would not be surprising if processes modifying the GPI-anchor attachment of PrP^C, resulting in altered structure or sorting/localization, or disturbing the integrity of lipid rafts may influence the substrate-protease interaction and alter the neuroprotective processing of PrP^C. In fact, it has been shown for other ADAM10 substrates mainly present in lipid rafts, that depletion of these microdomains significantly increased the proteolytic processing due to increased interaction with the protease (as active ADAM10 is preferentially found outside of rafts).[114-117] Moreover, attachment of a GPI-anchor to ADAM10 was shown to target the protease to lipid rafts, which resulted in altered processing of the amyloid precursor protein.[116] With regard to PrP^C more research is necessary to clarify whether manipulations of this kind might offer a treatment option for prion diseases and other proteinopathies.

Concluding Remarks

Increasing evidence locates PrP^C as a key player in mediating neurotoxic signaling not only in prion diseases but in other neurodegenerative diseases such as Alzheimer disease. Understanding the importance of membrane localization of PrP^C in lipid rafts

as well as how the anchorage of PrP^C can influence disease progression is of outstanding importance in order to develop further therapeutic strategies.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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References

1. RuddPM, MerryAH, WormaldMR, DwekRA. Glycosylation and prion protein.CurrOpinStructBiol2002; 12:578-86; PMID:12464308; http://dx.doi.org/10.1016/S0959-440X(02)00377-9
2. StahlN, BaldwinMA, TeplowDB, HoodL, GibsonBW, BurlingameAL, PrusinerSB. Structural studies of the scrapie prion protein using mass spectrometry and amino acid sequencing. Biochemistry1993; 32:1991-2002; PMID:8448158; http://dx.doi.org/10.1021/bi00059a016
3. PrusinerSB. Prions.ProcNatlAcadSci U S A1998; 95:13363-83; PMID:9811807; http://dx.doi.org/10.1073/pnas.95.23.13363
4. FujitaM, KinoshitaT. Structural remodeling of GPI anchors during biosynthesis and after attachment to proteins.FEBS Lett2010; 584:1670-7; PMID:19883648; http://dx.doi.org/10.1016/j.febslet.2009.10.079
5. FergusonMAJ, KinoshitaT, HartGW. Glycosylphosphatidylinositol Anchors. 2nd ed. Cold Spring Harbor: Cold Spring Harbor Laboratory Press; 2009. Chapter 11
6. PaulickMG, BertozziCR. The glycosylphosphatidylinositol anchor: a complex membrane-anchoring structure for proteins.Biochemistry2008; 47:6991-7000; PMID:18557633; http://dx.doi.org/10.1021/bi8006324
7. OrleanP, MenonAK. Thematic review series: lipid posttranslational modifications. GPI anchoring of protein in yeast and mammalian cells, or: how we learned to stop worrying and love glycophospholipids.J Lipid Res2007; 48:993-1011; PMID:17361015; http://dx.doi.org/10.1194/jlr.R700002-JLR200
8. MorandatS, BortolatoM, RouxB. Role of GPI-anchored enzyme in liposome detergent-resistance.J MembrBiol2003; 191:215-21; PMID:12571756; http://dx.doi.org/10.1007/s00232-002-1056-y
9. BarboniE, RiveroBP, GeorgeAJ, MartinSR, RenoupDV, HounsellEF, BarberPC, MorrisRJ. The glycophosphatidylinositol anchor affects the conformation of Thy-1 protein.J Cell Sci1995; 108:487-97; PMID:7539435
10. KukulanskyT, AbramovitchS, HollanderN. Cleavage of the glycosylphosphatidylinositol anchor affects the reactivity of thy-1 with antibodies.J Immunol1999; 162:5993-7; PMID:10229838
11. LeglerDF, DouceyMA, SchneiderP, ChapatteL, BenderFC, BronC. Differential insertion of GPI-anchored GFPs into lipid rafts of live cells.FASEB J2005; 19:73-5; PMID:15516372
12. MedofME, NagarajanS, TykocinskiML. Cell-surface engineering with GPI-anchored proteins.FASEB J1996; 10:574-86; PMID:8621057
13. LiuT, LiR, PanT, LiuD, PetersenRB, WongBS, GambettiP, SyMS. Intercellular transfer of the cellular prion protein.J BiolChem2002; 277:47671-8; PMID:12359724; http://dx.doi.org/10.1074/jbc.M207458200
14. VidugirieneJ, MenonAK. The GPI anchor of cell-surface proteins is synthesized on the cytoplasmic face of the endoplasmic reticulum.J Cell Biol1994; 127:333-41; PMID:7929579; http://dx.doi.org/10.1083/jcb.127.2.333
15. BrewisIA, FergusonMA, MehlertA, TurnerAJ, HooperNM. Structures of the glycosyl-phosphatidylinositol anchors of porcine and human renal membrane dipeptidase. Comprehensive structural studies on the porcine anchor and interspecies comparison of the glycan core structures.J BiolChem1995; 270:22946-56; PMID:7559431; http://dx.doi.org/10.1074/jbc.270.39.22946
16. MeriS, LehtoT, SuttonCW, TyyneläJ, BaumannM. Structural composition and functional characterization of soluble CD59: heterogeneity of the oligosaccharide and glycophosphoinositol (GPI) anchor revealed by laser-desorption mass spectrometric analysis.Biochem J1996; 316:923-35; PMID:8670172
17. StahlN, BaldwinMA, BurlingameAL, PrusinerSB. Identification of glycoinositol phospholipid linked and truncated forms of the scrapie prion protein. Biochemistry1990; 29:8879-84; PMID:1980209; http://dx.doi.org/10.1021/bi00490a001
18. BaldwinMA. Analysis of glycosylphosphatidylinositol protein anchors: the prion protein.Methods Enzymol2005; 405:172-87; PMID:16413315; http://dx.doi.org/10.1016/S0076-6879(05)05008-1
19. SimonsK, SampaioJL. Membrane organization and lipid rafts.Cold Spring HarbPerspectBiol2011; 3:a004697; PMID:21628426; http://dx.doi.org/10.1101/cshperspect.a004697
20. UdenfriendS, KodukulaK. How glycosylphosphatidylinositol-anchored membrane proteins are made.Annu Rev Biochem1995; 64:563-91; PMID:7574493; http://dx.doi.org/10.1146/annurev.bi.64.070195.003023
21. FujitaM, JigamiY. Lipid remodeling of GPI-anchored proteins and its function.BiochimBiophysActa2008; 1780:410-20; PMID:17913366; http://dx.doi.org/10.1016/j.bbagen.2007.08.009
22. LingwoodD, SimonsK. Lipid rafts as a membrane-organizing principle.Science2010; 327:46-50; PMID:20044567; http://dx.doi.org/10.1126/science.1174621
23. Tsui-PierchalaBA, EncinasM, MilbrandtJ, JohnsonEMJr.Lipid rafts in neuronal signaling and function.Trends Neurosci2002; 25:412-7; PMID:12127758; http://dx.doi.org/10.1016/S0166-2236(02)02215-4
24. StefanováI, HorejsíV, AnsoteguiIJ, KnappW, StockingerH. GPI-anchored cell-surface molecules complexed to protein tyrosine kinases.Science1991; 254:1016-9; PMID:1719635; http://dx.doi.org/10.1126/science.1719635
25. ChenY, VeraciniL, BenistantC, JacobsonK. The transmembrane protein CBP plays a role in transiently anchoring small clusters of Thy-1, a GPI-anchored protein, to the cytoskeleton.J Cell Sci2009; 122:3966-72; PMID:19825940; http://dx.doi.org/10.1242/jcs.049346
26. de HoopMJ, DottiCG. Membrane traffic in polarized neurons in culture.J Cell SciSuppl1993; 17:85-92; PMID:8144707; http://dx.doi.org/10.1242/jcs.1993.Supplement_17.13
27. van MeerG, SimonsK. Lipid polarity and sorting in epithelial cells.J Cell Biochem1988; 36:51-8; PMID:3277985; http://dx.doi.org/10.1002/jcb.240360106
28. BrownDA, CriseB, RoseJK. Mechanism of membrane anchoring affects polarized expression of two proteins in MDCK cells.Science1989; 245:1499-501; PMID:2571189; http://dx.doi.org/10.1126/science.2571189
29. LisantiMP, CarasIW, DavitzMA, Rodriguez-BoulanE. A glycophospholipid membrane anchor acts as an apical targeting signal in polarized epithelial cells.J Cell Biol1989; 109:2145-56; PMID:2478564; http://dx.doi.org/10.1083/jcb.109.5.2145
30. SarnataroD, PaladinoS, CampanaV, GrassiJ, NitschL, ZurzoloC. PrPC is sorted to the basolateral membrane of epithelial cells independently of its association with rafts.Traffic2002; 3:810-21; PMID:12383347; http://dx.doi.org/10.1034/j.1600-0854.2002.31106.x
31. PaladinoS, SarnataroD, PillichR, TivodarS, NitschL, ZurzoloC. Protein oligomerization modulates raft partitioning and apical sorting of GPI-anchored proteins.J Cell Biol2004; 167:699-709; PMID:15557121; http://dx.doi.org/10.1083/jcb.200407094
32. PaladinoS, LebretonS, TivodarS, CampanaV, TempreR, ZurzoloC. Different GPI-attachment signals affect the oligomerisation of GPI-anchored proteins and their apical sorting.J Cell Sci2008; 121:4001-7; PMID:19056670; http://dx.doi.org/10.1242/jcs.036038
33. PuigB, AltmeppenHC, ThurmD, GeissenM, ConradC, BraulkeT, GlatzelM. N-glycans and glycosylphosphatidylinositol-anchor act on polarized sorting of mouse PrP(C) in Madin-Darby canine kidney cells.PLoS One2011; 6:e24624; PMID:21931781; http://dx.doi.org/10.1371/journal.pone.0024624
34. MadoreN, SmithKL, GrahamCH, JenA, BradyK, HallS, MorrisR. Functionally different GPI proteins are organized in different domains on the neuronal surface.EMBO J1999; 18:6917-26; PMID:10601014; http://dx.doi.org/10.1093/emboj/18.24.6917
35. BrüggerB, GrahamC, LeibrechtI, MombelliE, JenA, WielandF, MorrisR. The membrane domains occupied by glycosylphosphatidylinositol-anchored prion protein and Thy-1 differ in lipid composition.J BiolChem2004; 279:7530-6; PMID:14660659; http://dx.doi.org/10.1074/jbc.M310207200
36. TivodarS, PaladinoS, PillichR, PrinettiA, ChigornoV, van MeerG, SonninoS, ZurzoloC. Analysis of detergent-resistant membranes associated with apical and basolateral GPI-anchored proteins in polarized epithelial cells.FEBS Lett2006; 580:5705-12; PMID:17007841; http://dx.doi.org/10.1016/j.febslet.2006.09.022
37. MironovAJr., LatawiecD, WilleH, Bouzamondo-BernsteinE, LegnameG, WilliamsonRA, BurtonD, DeArmondSJ, PrusinerSB, PetersPJ. Cytosolic prion protein in neurons.J Neurosci2003; 23:7183-93; PMID:12904479
38. GalvanC, CamolettoPG, DottiCG, AguzziA, LedesmaMD. Proper axonal distribution of PrP(C) depends on cholesterol-sphingomyelin-enriched membrane domains and is developmentally regulated in hippocampal neurons.Mol Cell Neurosci2005; 30:304-15; PMID:16139509; http://dx.doi.org/10.1016/j.mcn.2005.07.003
39. ChenR, KnezJJ, MerrickWC, MedofME. Comparative efficiencies of C-terminal signals of native glycophosphatidylinositol (GPI)-anchored proproteins in conferring GPI-anchoring.J Cell Biochem2001; 84:68-83; PMID:11746517; http://dx.doi.org/10.1002/jcb.1267

40. NicholsonTB, StannersCP. Specific inhibition of GPI-anchored protein function by homing and self-association of specific GPI anchors.J Cell Biol2006; 175:647-59; PMID:17101695; http://dx.doi.org/10.1083/jcb.200605001
41. NicholsonTB, StannersCP. Identification of a novel functional specificity signal within the GPI anchor signal sequence of carcinoembryonic antigen.J Cell Biol2007; 177:211-8; PMID:17438079; http://dx.doi.org/10.1083/jcb.200701158
42. WadsworthJD, HillAF, BeckJA, CollingeJ. Molecular and clinical classification of human prion disease.Br Med Bull2003; 66:241-54; PMID:14522862; http://dx.doi.org/10.1093/bmb/66.1.241
43. GuY, SinghA, BoseS, SinghN. Pathogenic mutations in the glycosylphosphatidylinositol signal peptide of PrP modulate its topology in neuroblastoma cells.Mol Cell Neurosci2008; 37:647-56; PMID:18325785; http://dx.doi.org/10.1016/j.mcn.2007.08.018
44. GuizzuntiG, ZurzoloC. The fate of PrP GPI-anchor signal peptide is modulated by P238S pathogenic mutation.Traffic2014; 15:78-93; PMID:24112521; http://dx.doi.org/10.1111/tra.12126
45. BorcheltDR, TaraboulosA, PrusinerSB. Evidence for synthesis of scrapie prion proteins in the endocytic pathway.J BiolChem1992; 267:16188-99; PMID:1353761
46. BérangerF, MangéA, GoudB, LehmannS. Stimulation of PrP(C) retrograde transport toward the endoplasmic reticulum increases accumulation of PrP(Sc) in prion-infected cells.J BiolChem2002; 277:38972-7; PMID:12163492; http://dx.doi.org/10.1074/jbc.M205110200
47. MarijanovicZ, CaputoA, CampanaV, ZurzoloC. Identification of an intracellular site of prion conversion.PLoSPathog2009; 5:e1000426; PMID:19424437; http://dx.doi.org/10.1371/journal.ppat.1000426
48. BaronGS, WehrlyK, DorwardDW, ChesebroB, CaugheyB. Conversion of raft associated prion protein to the protease-resistant state requires insertion of PrP-res (PrP(Sc)) into contiguous membranes. EMBO J2002; 21:1031-40; PMID:11867531; http://dx.doi.org/10.1093/emboj/21.5.1031
49. GooldR, RabbanianS, SuttonL, AndreR, AroraP, MoongaJ, ClarkeAR, SchiavoG, JatP, CollingeJ, et al.Rapid cell-surface prion protein conversion revealed using a novel cell system.Nat Commun2011; 2:281; PMID:21505437; http://dx.doi.org/10.1038/ncomms1282
50. GooldR, McKinnonC, RabbanianS, CollingeJ, SchiavoG, TabriziSJ. Alternative fates of newly formed PrPSc upon prion conversion on the plasma membrane.J Cell Sci2013; 126:3552-62; PMID:23813960; http://dx.doi.org/10.1242/jcs.120477
51. TaraboulosA, ScottM, SemenovA, AvrahamiD, LaszloL, PrusinerSB. Cholesterol depletion and modification of COOH-terminal targeting sequence of the prion protein inhibit formation of the scrapie isoform.J Cell Biol1995; 129:121-32; PMID:7698979; http://dx.doi.org/10.1083/jcb.129.1.121
52. MangéA, NishidaN, MilhavetO, McMahonHE, CasanovaD, LehmannS. Amphotericin B inhibits the generation of the scrapie isoform of the prion protein in infected cultures.J Virol2000; 74:3135-40; PMID:10708429; http://dx.doi.org/10.1128/JVI.74.7.3135-3140.2000
53. MarellaM, LehmannS, GrassiJ, ChabryJ. Filipin prevents pathological prion protein accumulation by reducing endocytosis and inducing cellular PrP release.J BiolChem2002; 277:25457-64; PMID:11994310; http://dx.doi.org/10.1074/jbc.M203248200
54. TaraboulosA, ScottM, SemenovA, AvrahamiD, LaszloL, PrusinerSB. Cholesterol depletion and modification of COOH-terminal targeting sequence of the prion protein inhibit formation of the scrapie isoform.J Cell Biol1995; 129:121-32; PMID:7698979; http://dx.doi.org/10.1083/jcb.129.1.121
55. KociskoDA, ComeJH, PriolaSA, ChesebroB, RaymondGJ, LansburyPT, CaugheyB. Cell-free formation of protease-resistant prion protein. Nature1994; 370:471-4; PMID:7913989; http://dx.doi.org/10.1038/370471a0
56. McNallyKL, WardAE, PriolaSA. Cells expressing anchorless prion protein are resistant to scrapie infection.J Virol2009; 83:4469-75; PMID:19225008; http://dx.doi.org/10.1128/JVI.02412-08
57. PriolaSA, McNallyKL. The role of the prion protein membrane anchor in prion infection.Prion2009; 3:134-8; PMID:19786843; http://dx.doi.org/10.4161/pri.3.3.9771
58. SpeareJO, OfferdahlDK, HasenkrugA, CarmodyAB, BaronGS. GPI anchoring facilitates propagation and spread of misfolded Sup35 aggregates in mammalian cells.EMBO J2010; 29:782-94; PMID:20057357; http://dx.doi.org/10.1038/emboj.2009.392
59. Fernández-BorgesN, ChianiniF, ErañaH, VidalE, EatonSL, PintadoB, FinlaysonJ, DagleishMP, CastillaJ. Naturally prion resistant mammals: a utopia?Prion2012; 6:425-9; PMID:22954650; http://dx.doi.org/10.4161/pri.22057
60. NisbetRM, HarrisonCF, LawsonVA, MastersCL, CappaiR, HillAF.Residues surrounding the glycosylphosphatidylinositol anchor attachment site of PrP modulate prion infection: insight from the resistance of rabbits to prion disease.J Virol2010; 84:6678-86; PMID:20427543; http://dx.doi.org/10.1128/JVI.02709-09
61. JeffreyM, McGovernG, SisóS, GonzálezL. Cellular and sub-cellular pathology of animal prion diseases: relationship between morphological changes, accumulation of abnormal prion protein and clinical disease.ActaNeuropathol2011; 121:113-34; PMID:20532540; http://dx.doi.org/10.1007/s00401-010-0700-3
62. BüelerH, AguzziA, SailerA, GreinerRA, AutenriedP, AguetM, WeissmannC. Mice devoid of PrP are resistant to scrapie.Cell1993; 73:1339-47; PMID:8100741; http://dx.doi.org/10.1016/0092-8674(93)90360-3
63. MalluccigG, DickinsonA, LinehanJ, KlöhnPC, BrandnerS, CollingeJ. Depleting neuronal PrP in prion infection prevents disease and reverses spongiosis.Science2003; 302:871-4; PMID:14593181; http://dx.doi.org/10.1126/science.1090187
64. SandbergMK, Al-DoujailyH, SharpsB, ClarkeAR, CollingeJ. Prion propagation and toxicity in vivo occur in two distinct mechanistic phases. Nature2011; 470:540-2; PMID:21350487; http://dx.doi.org/10.1038/nature09768
65. ChesebroB, RaceB, Meade-WhiteK, LacasseR, RaceR, KlingebornM, StriebelJ, DorwardD, McGovernG, JeffreyM. Fatal transmissible amyloid encephalopathy: a new type of prion disease associated with lack of prion protein membrane anchoring. PLoSPathog2010; 6:e1000800; PMID:20221436; http://dx.doi.org/10.1371/journal.ppat.1000800
66. FasanoC, CampanaV, ZurzoloC. Prions: protein only or something more? Overview of potential prion cofactors.J MolNeurosci2006; 29:195-214; PMID:17085779; http://dx.doi.org/10.1385/JMN:29:3:195
67. TaylorDR, WhitehouseIJ, HooperNM.Glypican-1 mediates both prion protein lipid raft association and disease isoform formation.PLoSPathog2009; 5:e1000666; PMID:19936054; http://dx.doi.org/10.1371/journal.ppat.1000666
68. FivazM, VilboisF, ThurnheerS, PasqualiC, AbramiL, BickelPE, PartonRG, van der GootFG. Differential sorting and fate of endocytosed GPI-anchored proteins.EMBO J2002; 21:3989-4000; PMID:12145200; http://dx.doi.org/10.1093/emboj/cdf398
69. SunyachC, JenA, DengJ, FitzgeraldKT, FrobertY, GrassiJ, McCaffreyMW, MorrisR. The mechanism of internalization of glycosylphosphatidylinositol-anchored prion protein.EMBO J2003; 22:3591-601; PMID:12853474; http://dx.doi.org/10.1093/emboj/cdg344
70. TaylorDR, HooperNM. The low-density lipoprotein receptor-related protein 1 (LRP1) mediates the endocytosis of the cellular prion protein.Biochem J2007; 402:17-23; PMID:17155929; http://dx.doi.org/10.1042/BJ20061736
71. ParkynCJ, VermeulenEG, MootoosamyRC, SunyachC, JacobsenC, OxvigC, MoestrupS, LiuQ, BuG, JenA, et al.LRP1 controls biosynthetic and endocytic trafficking of neuronal prion protein.J Cell Sci2008; 121:773-83; PMID:18285446; http://dx.doi.org/10.1242/jcs.021816
72. SarnataroD, CaputoA, CasanovaP, PuriC, PaladinoS, TivodarSS, CampanaV, TacchettiC, ZurzoloC. Lipid rafts and clathrin cooperate in the internalization of PrP in epithelial FRT cells.PLoS One2009; 4:e5829; PMID:19503793; http://dx.doi.org/10.1371/journal.pone.0005829
73. LindenR, MartinsVR, PradoMA, CammarotaM, IzquierdoI, BrentaniRR. Physiology of the prion protein.Physiol Rev2008; 88:673-728; PMID:18391177; http://dx.doi.org/10.1152/physrev.00007.2007
74. BiasiniE, TurnbaughJA, UnterbergerU, HarrisDA. Prion protein at the crossroads of physiology and disease.Trends Neurosci2012; 35:92-103; PMID:22137337; http://dx.doi.org/10.1016/j.tins.2011.10.002
75. BateC, WilliamsA. Role of glycosylphosphatidylinositols in the activation of phospholipase A2 and the neurotoxicity of prions.J Gen Virol2004; 85:3797-804; PMID:15557253; http://dx.doi.org/10.1099/vir.0.80366-0
76. BateC, TayebiM, WilliamsA. Phospholipase A2 inhibitors protect against prion and Abeta mediated synapse degeneration.MolNeurodegener2010; 5:13; PMID:20374666; http://dx.doi.org/10.1186/1750-1326-5-13
77. BrownWJ, ChambersK, DoodyA. Phospholipase A2 (PLA2) enzymes in membrane trafficking: mediators of membrane shape and function.Traffic2003; 4:214-21; PMID:12694560; http://dx.doi.org/10.1034/j.1600-0854.2003.00078.x
78. BateC, WilliamsA. Neurodegeneration induced by clustering of sialylatedglycosylphosphatidylinositols of prion proteins.J BiolChem2012; 287:7935-44; PMID:22262833; http://dx.doi.org/10.1074/jbc.M111.275743
79. BateC, WilliamsA. Monoacylated cellular prion protein modifies cell membranes, inhibits cell signaling, and reduces prion formation.J BiolChem2011; 286:8752-8; PMID:21212283; http://dx.doi.org/10.1074/jbc.M110.186833
80. BateC, WilliamsA. The cellular prion protein with a monoacylatedglycosylphosphatidylinositol anchor modifies cell membranes, inhibits cell signaling and reduces prion formation.Prion2011; 5:65-8; PMID:21738009; http://dx.doi.org/10.4161/pri.5.2.16095
81. KhosravaniH, ZhangY, TsutsuiS, HameedS, AltierC, HamidJ, ChenL, VillemaireM, AliZ, JirikFR, et al. Prion protein attenuates excitotoxicity by inhibiting NMDA receptors.J Cell Biol2008; 181:551-65; PMID:18443219; http://dx.doi.org/10.1083/jcb.200711002
82. WangYT, SalterMW. Regulation of NMDA receptors by tyrosine kinases and phosphatases.Nature1994; 369:233-5; PMID:7514272; http://dx.doi.org/10.1038/369233a0

83. SalterMW, KaliaLV. Src kinases: a hub for NMDA receptor regulation.Nat Rev Neurosci2004; 5:317-28; PMID:15034556; http://dx.doi.org/10.1038/nrn1368
84. SwanwickCC, ShapiroME, YiZ, ChangK, WentholdRJ. NMDA receptors interact with flotillin-1 and -2, lipid raft-associated proteins.FEBS Lett2009; 583:1226-30; PMID:19298817; http://dx.doi.org/10.1016/j.febslet.2009.03.017
85. PonceJ, de la OssaNP, HurtadoO, MillanM, ArenillasJF, DávalosA, GasullT. Simvastatin reduces the association of NMDA receptors to lipid rafts: a cholesterol-mediated effect in neuroprotection. Stroke2008; 39:1269-75; PMID:18323503; http://dx.doi.org/10.1161/STROKEAHA.107.498923
86. Mouillet-RichardS, ErmonvalM, ChebassierC, LaplancheJL, LehmannS, LaunayJM, KellermannO. Signal transduction through prion protein. Science2000; 289:1925-8; PMID:10988071; http://dx.doi.org/10.1126/science.289.5486.1925
87. LaurénJ, GimbelDA, NygaardHB, GilbertJW, StrittmatterSM. Cellular prion protein mediates impairment of synaptic plasticity by amyloid-beta oligomers.Nature2009; 457:1128-32; PMID:19242475; http://dx.doi.org/10.1038/nature07761
88. UmJW, NygaardHB, HeissJK, KostylevMA, StagiM, VortmeyerA, WisniewskiT, GuntherEC, StrittmatterSM. Alzheimer amyloid-β oligomer bound to postsynaptic prion protein activates Fyn to impair neurons.Nat Neurosci2012; 15:1227-35; PMID:22820466; http://dx.doi.org/10.1038/nn.3178
89. UmJW, StrittmatterSM. Amyloid-β induced signaling by cellular prion protein and Fyn kinase in Alzheimer disease.Prion2013; 7:37-41; PMID:22987042; http://dx.doi.org/10.4161/pri.22212
90. LarsonME, LesnéSE. Soluble Aβ oligomer production and toxicity.J Neurochem2012; 120(Suppl 1):125-39; PMID:22121920; http://dx.doi.org/10.1111/j.1471-4159.2011.07478.x
91. ResenbergerUK, HarmeierA, WoernerAC, GoodmanJL, MüllerV, KrishnanR, VabulasRM, KretzschmarHA, LindquistS, HartlFU, et al.The cellular prion protein mediates neurotoxic signalling of β-sheet-rich conformers independent of prion replication.EMBO J2011; 30:2057-70; PMID:21441896; http://dx.doi.org/10.1038/emboj.2011.86
92. PradinesE, Hernandez-RappJ, Villa-DiazA, DakowskiC, Ardila-OsorioH, HaikS, SchneiderB, LaunayJM, KellermannO, TorresJM, et al.Pathogenic prions deviate PrP(C) signaling in neuronal cells and impair A-beta clearance.Cell Death Dis2013; 4:e456; PMID:23303130; http://dx.doi.org/10.1038/cddis.2012.195
93. RamboldAS, MüllerV, RonU, Ben-TalN, WinklhoferKF, TatzeltJ. Stress-protective signalling of prion protein is corrupted by scrapie prions.EMBO J2008; 27:1974-84; PMID:18566584; http://dx.doi.org/10.1038/emboj.2008.122
94. ChenSG, TeplowDB, ParchiP, TellerJK, GambettiP, Autilio-GambettiL. Truncated forms of the human prion protein in normal brain and in prion diseases.J BiolChem1995; 270:19173-80; PMID:7642585; http://dx.doi.org/10.1074/jbc.270.32.19173
95. TaylorDR, ParkinET, CocklinSL, AultJR, AshcroftAE, TurnerAJ, HooperNM. Role of ADAMs in the ectodomain shedding and conformational conversion of the prion protein.J BiolChem2009; 284:22590-600; PMID:19564338; http://dx.doi.org/10.1074/jbc.M109.032599
96. AltmeppenHC, ProxJ, PuigB, KluthMA, BernreutherC, ThurmD, JorissenE, PetrowitzB, BartschU, De StrooperB, et al.Lack of a-disintegrin-and-metalloproteinase ADAM10 leads to intracellular accumulation and loss of shedding of the cellular prion protein in vivo.MolNeurodegener2011; 6:36; PMID:21619641; http://dx.doi.org/10.1186/1750-1326-6-36
97. SunyachC, CisseMA, da CostaCA, VincentB, CheclerF. The C-terminal products of cellular prion protein processing, C1 and C2, exert distinct influence on p53-dependent staurosporine-induced caspase-3 activation.J BiolChem2007; 282:1956-63; PMID:17121821; http://dx.doi.org/10.1074/jbc.M609663200
98. WestergardL, TurnbaughJA, HarrisDA. A naturally occurring C-terminal fragment of the prion protein (PrP) delays disease and acts as a dominant-negative inhibitor of PrPSc formation.J BiolChem2011; 286:44234-42; PMID:22025612; http://dx.doi.org/10.1074/jbc.M111.286195
99. AltmeppenHC, ProxJ, PuigB, DohlerF, FalkerC, KrasemannS, GlatzelM. Roles of endoproteolytic α-cleavage and shedding of the prion protein in neurodegeneration.FEBS J2013; 280:4338-47; PMID:23413979; http://dx.doi.org/10.1111/febs.12196
100. MeierP, GenoudN, PrinzM, MaissenM, RülickeT, ZurbriggenA, RaeberAJ, AguzziA. Soluble dimeric prion protein binds PrP(Sc) in vivo and antagonizes prion disease.Cell2003; 113:49-60; PMID:12679034; http://dx.doi.org/10.1016/S0092-8674(03)00201-0
101. Guillot-SestierMV, SunyachC, DruonC, ScarzelloS, CheclerF. The alpha-secretase-derived N-terminal product of cellular prion, N1, displays neuroprotective function in vitro and in vivo.J BiolChem2009; 284:35973-86; PMID:19850936; http://dx.doi.org/10.1074/jbc.M109.051086
102. Guillot-SestierMV, CheclerF. α-Secretase-derived cleavage of cellular prion yields biologically active catabolites with distinct functions.Neurodegener Dis2012; 10:294-7; PMID:22261541; http://dx.doi.org/10.1159/000333804
103. CalellaAM, FarinelliM, NuvoloneM, MiranteO, MoosR, FalsigJ, MansuyIM, AguzziA. Prion protein and Abeta-related synaptic toxicity impairment. EMBO Mol Med2010; 2:306-14; PMID:20665634; http://dx.doi.org/10.1002/emmm.201000082
104. BélandM, MotardJ, BarbarinA, RoucouX. PrP(C) homodimerization stimulates the production of PrPC cleaved fragments PrPN1 and PrPC1.J Neurosci2012; 32:13255-63; PMID:22993441; http://dx.doi.org/10.1523/JNEUROSCI.2236-12.2012
105. NieznanskiK, ChoiJK, ChenS, SurewiczK, SurewiczWK. Soluble prion protein inhibits amyloid-β (Aβ) fibrillization and toxicity.J BiolChem2012; 287:33104-8; PMID:22915585; http://dx.doi.org/10.1074/jbc.C112.400614
106. FluhartyBR, BiasiniE, StravalaciM, SclipA, DiomedeL, BalducciC, La VitolaP, MessaM, ColomboL, ForloniG, et al.An N-terminal fragment of the prion protein binds to amyloid-β oligomers and inhibits their neurotoxicity in vivo.J BiolChem2013; 288:7857-66; PMID:23362282; http://dx.doi.org/10.1074/jbc.M112.423954
107. OstapchenkoVG, BeraldoFH, GuimarãesAL, MishraS, GuzmanM, FanJ, MartinsVR, PradoVF, PradoMA. Increased prion protein processing and expression of metabotropic glutamate receptor 1 in a mouse model of Alzheimer's disease.J Neurochem2013; 127:415-25; PMID:23651058; http://dx.doi.org/10.1111/jnc.12296
108. AltmeppenHC, PuigB, DohlerF, ThurmDK, FalkerC, KrasemannS, GlatzelM. Proteolytic processing of the prion protein in health and disease.Am J Neurodegener Dis2012; 1:15-31; PMID:23383379
109. LiangJ, KongQ. α-Cleavage of cellular prion protein. Prion2012; 6:453-60; PMID:23052041; http://dx.doi.org/10.4161/pri.22511
110. McDonaldAJ, DibbleJP, EvansEG, MillhauserGL.A New Paradigm for Enzymatic Control of α-Cleavage and β-Cleavage of the Prion Protein.J BiolChem2014; 289:803-13; PMID:24247244; http://dx.doi.org/10.1074/jbc.M113.502351
111. WikL, KlingebornM, WillanderH, LinneT. Separate mechanisms act concurrently to shed and release the prion protein from the cell.Prion2012; 6:498-509; PMID:23093798; http://dx.doi.org/10.4161/pri.22588
112. WalmsleyAR, WattNT, TaylorDR, PereraWS, HooperNM. alpha-cleavage of the prion protein occurs in a late compartment of the secretory pathway and is independent of lipid rafts.Mol Cell Neurosci2009; 40:242-8; PMID:19056496; http://dx.doi.org/10.1016/j.mcn.2008.10.012
113. LiangJ, WangW, SorensenD, MedinaS, IlchenkoS, KiselarJ, SurewiczWK, BoothSA, KongQ. Cellular prion protein regulates its own α-cleavage through ADAM8 in skeletal muscle.J BiolChem2012; 287:16510-20; PMID:22447932; http://dx.doi.org/10.1074/jbc.M112.360891
114. KojroE, GimplG, LammichS, MarzW, FahrenholzF. Low cholesterol stimulates the nonamyloidogenic pathway by its effect on the alpha -secretase ADAM 10.ProcNatlAcadSci U S A2001; 98:5815-20; PMID:11309494; http://dx.doi.org/10.1073/pnas.081612998
115. KojroE, FügerP, PrinzenC, KanarekAM, RatD, EndresK, FahrenholzF, PostinaR. Statins and the squalene synthase inhibitor zaragozic acid stimulate the non-amyloidogenic pathway of amyloid-beta protein precursor processing by suppression of cholesterol synthesis.J Alzheimers Dis2010; 20:1215-31; PMID:20413873
116. HarrisB, PereiraI, ParkinE. Targeting ADAM10 to lipid rafts in neuroblastoma SH-SY5Y cells impairs amyloidogenic processing of the amyloid precursor protein.Brain Res2009; 1296:203-15; PMID:19679113; http://dx.doi.org/10.1016/j.brainres.2009.07.105
117. MuraiT, MaruyamaY, MioK, NishiyamaH, SugaM, SatoC. Low cholesterol triggers membrane microdomain-dependent CD44 shedding and suppresses tumor cell migration.J BiolChem2011; 286:1999-2007; PMID:21087933; http://dx.doi.org/10.1074/jbc.M110.184010
118. RushworthJV, GriffithsHH, WattNT, HooperNM. Prion protein-mediated toxicity of amyloid-β oligomers requires lipid rafts and the transmembrane LRP1.J BiolChem2013; 288:8935-51; PMID:23386614; http://dx.doi.org/10.1074/jbc.M112.400358
119. UmJW, KaufmanAC, KostylevM, HeissJK, StagiM, TakahashiH, KerriskME, VortmeyerA, WisniewskiT, KoleskeAJ, et al.Metabotropic glutamate receptor 5 is a coreceptor for Alzheimer aβ oligomer bound to cellular prion protein.Neuron2013; 79:887-902; PMID:24012003; http://dx.doi.org/10.1016/j.neuron.2013.06.036