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Review

Prion proteins and their impact on memory: A complex relationship

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ABSTRACT

Prion proteins are significant proteins located on the surface of mammalian cells, closely associated with the nervous system. They were first discovered in the context of fatal neurodegenerative diseases known as prion diseases. In these diseases, a pathological form of the cellular prion protein, known as scrapie prion protein, which exhibits a beta-sheet-rich structure, is observed. Although the exact function of prion proteins is not yet fully understood, there is growing speculation about their potential role in memory formation and long-term memory processes. In this review, we address prion proteins, prion-like proteins, and their relationship with memory processes.

Keywords: Memory, memory formation, prion diseases, prion-like proteins, prion protein.

The cellular prion protein (PrP^C) is a surface protein found in all mammalian tissues and is encoded by the PRNP gene, located on chromosome 20 in humans and chromosome 2 in mice. The PrP^C is widely expressed in the central nervous system (CNS), particularly in adult neurons and glial cells during early development. After translation and co-translational extrusion into the lumen of the endoplasmic reticulum (ER), the PrP^C protein adopts its physiological structure, which consists of two distinct regions: a long N-terminal tail containing four or five octapeptide repeats, and a globular C-terminal domain comprising three alpha-helices (α-helices) and three beta-strands (β-strands). The N-terminal region also includes a series of repeat sequences containing histidine residues that aid in coordinating the binding of divalent metal ions. Meanwhile, the C-terminal region serves as the site for post-translational modifications in PrP^C.[1-6] Overall, PrP^C exhibits an unstructured conformation primarily composed of α-helices.[7]

The PrP^C is initially synthesized as a precursor protein (pre-pro-PrP) consisting of 253 amino acids. This synthesized protein contains a signal peptide at its N-terminus and a glycosylphosphatidylinositol (GPI) anchor signal sequence at its C-terminus. The signal peptide directs the pre-pro-PrP to the ER, where the N-terminal flexible tail is first cleaved. Subsequently, the protein loses the GPI signal peptide at residue 230 in the C-terminal region to acquire a GPI anchor. The removal of both signal sequences reduces the PrP protein to 208 amino acids. The resulting pro-PrP is then transported to the Golgi apparatus, where it undergoes N-linked glycosylation at Asn181 and Asn197 during its transit. Upon reaching the Golgi, the addition of a GPI anchor facilitates its attachment to the plasma membrane before being delivered to the cell surface.[8-11]

When examining post-translational modifications, several cleavage events are observed, with four of these cleavages appearing to be conserved.[6] These four conserved processes are referred to as α-cleavage, β-cleavage, gamma (γ)-cleavage, and

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shedding.[12] The process known as α-cleavage occurs under physiological conditions in the central hydrophobic region of mature PrP^C. It is the major proteolytic event that produces C1 (~16 kDa) fragments, which accumulate in the plasma membrane. Depending on the cell type and brain region, C1 fragments constitute 5-50% of the total PrP^C.[12,13] In humans, the α-cleavage occurs within the amino acid sequences spanning positions 106-126.[14] As a result of α-cleavage, two fragments, N1 (~11 kDa) and C (~18 kDa), are produced. For N1, neuroprotective functions have been suggested. Recently, it has been shown that the expression of C1 inhibits prion replication in mice and has a protective effect.[12,15]

β-cleavage occurs at the end of the octapeptide repeat region and is similar to α-cleavage, but it typically takes place under pathological conditions. In the human sequence, it occurs around the 90th amino acid position. It is believed that β-cleavage has a protective effect under oxidative stress. As a result of this cleavage, the N2 (~9 kDa) and C2 (~20 kDa) fragments are produced. However, unlike the C1/N1 fragments derived from α-cleavage, there is no experimental evidence supporting the physiological function of the C2/N2 fragments.[6,12,13]

A third physiological cleavage of PrP^C occurs near the GPI anchor and results in the release of nearly full-length protein from the plasma membrane. This cleavage takes place close to the C-terminus. It leads to the shedding of PrP into the extracellular space, leaving only a few amino acid residues remaining on the cell surface.[12,13] The process of releasing the extracellular domains of membrane-bound proteins through proteolytic cleavage is referred to as shedding.[16] Shedding PrP was first identified in the preparations of prion-infected hamster brains. Its physiological function is not fully understood, but it has been suggested that it could serve as a good substrate for prion replication. It is also believed to provide a promising and effective target for the treatment of various pathological conditions.[12,17,18]

Finally, when the nonglycosylated PrP^C undergoes γ-cleavage, it produces the soluble N3 (~20 kDa) and a short C3 (~5 kDa) fragment.[19] The cleavage is likely to occur in a region between amino acids 170-200, immediately N-terminal to the first N-glycosylation site, and it is believed to be mediated by a metalloprotease. The increased expression of C3 in brain samples from Creutzfeldt-Jakob disease (CJD) may indicate that γ-cleavage is pathophysiological in nature.[6] These post-translational modifications result in the formation of different membrane-bound or shed PrP^C fragments.[12]

Experiments have shown that the N-terminal region plays a role in neurodegeneration, while the C-terminal region has the ability to prevent neurodegeneration. Further research has revealed that the C-terminal region can regulate the N-terminal region through direct interaction.[20]

The PrP^C is typically found on the cell surface, and its sequence contains potential regions for N-linked glycosylation at residues 187 and 197. It can exist in three forms: monoglycosylated, diglycosylated, or unglycosylated. Its expression is particularly observed in nerve cells, and all three forms can be detected in whole brain homogenates.[21,22] In a study conducted on humans, quantitative transcript analysis of 27 different tissues from 95 individuals revealed that the prion gene PRNP is widely expressed in all 27 human tissues, in addition to mitochondria. The highest expression levels were found in the brain, particularly in nerve tissues, followed by the ovaries, prostate, heart, gallbladder, endometrium, adrenal glands, bladder, thyroid, testes, skin, esophagus, and lungs.[23,24] Furthermore, the independent transmission of prion conformers during chromatin-bound information separation, as well as their passage through both mitotic and meiotic divisions, has led to the hypothesis that prion proteins could be epigenetic elements.[25]

The PrP^C protein has two transmembrane forms, which are referred to as $^{Ntm}PrP^C$ and $^{Ctm}PrP^C$.[26] The $^{Ctm}PrP^C$ and $^{Ntm}PrP^C$ are formed when some PrP molecules adopt orientations where either the C-terminus or N-terminus faces opposite directions relative to the ER membrane, with the respective terminus either facing the ER lumen or the cytoplasm. However, the exact mechanisms behind the formation of all these forms remain unclear.[27]

Functions of prion protein

Although its physiological functions have not been fully elucidated, several studies have linked the overexpression of $^{Ctm}PrP^{C}$ with neurotoxicity.[28] However, there are studies suggesting that PrP^{C} may play a significant role in cancer treatment in the future.[29,30]

There is also strong evidence supporting the close relationship between PrP^{C} and stem cells. PrP^{C} is expressed in various embryonic stem cells and has been associated with the proliferation and self-renewal of stem cells.[31] The PrP^{C} expression is regulated according to the degree of stem cell differentiation and is involved in signaling pathways that play a role in the formation of various cell types.[32] In a study conducted by Siberchicot et al.[33] on mice, it was suggested that PrP^{C} protein may play a role in the expansion of hematopoietic stem cells during aging.

It is known that PrP^{C} protein plays a role in various processes, including neuronal differentiation, neuroprotection, signal transduction, and cell adhesion.[7] Knockout methods of PrP^{C} provide strong evidence for its neuroprotective functions.[34] In the human forebrain, PrP^{C} protein begins to be expressed at the 11^{th} week of gestation and continues until the end of pregnancy. This expression primarily occurs along axonal pathways, suggesting that PrP^{C} may play a role in axonal growth.[32]

Although studies on PrP^{C} have primarily focused on the nervous system, recent evidence shows that cellular PrP^{C} not only regulates stem cell renewal but also modulates proliferation and apoptosis resistance in cancer cells.[35] Additionally, other studies have reported high expression of the PRNP gene in cancer tissues.[36]

When misfolded proteins exceed the level that the ER can tolerate, a signaling pathway known as the unfolded protein response (UPR) is triggered.[37] The UPR is also known as the ER stress response.[38] In cells, the role of UPR is to maintain ER homeostasis by reducing the load of misfolded proteins.[39] In a study conducted by Gao et al.[40] on lung cancer patients, it was suggested that PrP^{C} contributes to the pathogenesis of lung cancer by activating the UPR, which is a response that alleviates ER stress.

The term "prion-like misfolding" is also considered to be an underlying mechanism in neurodegenerative diseases such as Alzheimer's and Parkinson's. However, much remains unknown about the fundamental biology of prions.[41]

PRION DISEASES

Historically, the first cellular prion protein, PrP^{C}, was discovered as the normal host counterpart of the infectious agent responsible for transmissible spongiform encephalopathies, namely the pathogenic scrapie prion protein (PrP^{Sc}).[42] Prion diseases are a result of the regular accumulation of GPI-anchored PrP^{Sc} protein expressed on the cell surface.[43] The PrP^{Sc} is an isoform of PrP^{C} that is self-propagating. This protein is encoded by the host but its misfolded or post-translational forms are the cause of the disease. The diseased PrP^{Sc} protein tends to alter the α-conformational conversion of healthy PrP^{C}, and thus, PrP^{C} expression is essential for the pathogenesis of prion diseases. In the absence of PrP^{C}, PrP^{Sc} formation is halted, and existing PrP^{Sc} is cleared by an unknown mechanism.[44-47] Additionally, in prion vaccine studies conducted on PrP^{C} knockout mice, it was observed that the mice did not develop prion diseases, providing evidence for the requirement of PrP^{C} for the propagation of PrP^{Sc}.[48] The PrP^{Sc} contains a high β-sheet content. Compared to PrP^{C}, which primarily exhibits an α-helix structure, PrP^{Sc} is resistant to proteases, and its β-sheet content makes it prone to aggregation.[49,50]

Prion diseases are distinct from other neurodegenerative diseases due to their transmissibility between individuals, as well as the existence of sporadic, genetic, and acquired forms.[51] Human prion diseases include the following: CJD, Gerstmann-Sträussler-Scheinker syndrome, and fatal familial insomnia.[44] These diseases are characterized by the accumulation of PrP^{Sc} in the brain, spongiform neurodegeneration, and neuronal cell loss. Approximately 15% of these cases are genetic. The genetic nature of 15% of cases may provide opportunities for early therapeutic intervention to delay or prevent the disease.[52,53]

In prion diseases, activation of microglia and astrocytes is observed before neuronal death or neuronal damage occurs.[54] In a study by Aguzzi and Zhu,[55] they suggested that microglia play a neuroprotective role in prion diseases.

The clinical features of this disease can vary, but common signs in the CNS include the accumulation of abnormally folded, protease-resistant prion protein, astrogliosis, microgliosis, neuroinflammation, and neurodegeneration. All prion diseases are fatal, and there is currently no treatment available.[44,54]

PRION PROTEINS AND MEMORY

Memory, prion, and prion-like proteins

Short-term (STM) and long-term memories (LTM) are closely linked. Information received from the environment and retained in the short term eventually forms long-term memories. However, past experiences influence our short-term memories.[56] Short-term memories last from minutes to hours, while LTM can persist from days to weeks. One of the key differences between LTM and STM is that long-term memory requires the activation of new gene expression. However, it is not only the new gene expression that is essential, but also the translation of dormant messenger ribonucleic acids (mRNAs) stored in synapses, which are induced by experience. Protein synthesis induced by experience is necessary for LTM. To consolidate long-term memory, both cellular and local mRNA translation must occur, with the latter ensuring the spatiotemporal regulation of gene expression.[57,58]

Although protein synthesis in synapses is necessary for long-term memory, the theory proposed by Tompa and Friedrich[59] in 1998 addresses how memory can last for days or months despite the rapid degradation of proteins. Their theory suggests that non-toxic prions involved in memory can self-renew indefinitely and catalyze the conformational conversion of newly synthesized proteins into prion forms.[59]

The results of a study by Leighton et al.[60] in zebrafish suggest that prion protein is essential for learning and memory functions in zebrafish. The PrP^C can contribute to memory formation through various mechanisms, and its conserved role in learning and memory is supported.

Additionally, Ondrejcak et al.[61] noted that amyloid β-oligomers, by binding to PrP^C, rapidly and strongly inhibit long-term potentiation, which includes synaptic activity-dependent persistent strengthening. Similarly, they highlighted that prion protein is required for the inhibition of long-term depression associated with synaptic weakening, mediated by soluble tau aggregates.

Prion-like domains (PrLDs) belong to the class of intrinsically disordered regions (IDRs). The IDRs can be defined as regions that do not adopt stable three-dimensional structures and tend to serve as centers for biomolecular complexes. They have low sequence complexity and are rich in glutamine and asparagine. These domains are frequently found among regulatory molecules and RNA-binding proteins. However, the physiological role of PrLDs remains unclear.[62,63]

The addition of this domain to non-harmful proteins is sufficient to confer prion-like behavior. Approximately 70 human RNA-binding proteins (RBPs) contain PrLDs.[64] Polypeptides containing similar PrLDs are generally referred to as prion-like proteins.[65] These regions may play a role in adapting to changing environmental conditions, immune responses, and memory formation.[66] The removal of these PrLD regions results in the prion protein losing its prion properties.[67]

In vertebrates, cytoplasmic polyadenylation element binding proteins (CPEBs) regulate translation in the brain and are part of a family of four RNA-binding proteins responsible for controlling various aspects of higher cognitive functions. The CPEB forms are “prion-like” motifs capable of templating other soluble CPEB molecules, transforming them into a prion form that can self-propagate.[59] The understanding of translational control critical for memory formation began with the identification of molecules that affect the 5' untranslated region (UTR) and 3’UTR regions of mRNAs. Generally, research on the translational control underlying memory has primarily focused on cap-dependent mechanisms. A tRNA and the eIF2 complex bind to the 5’UTR, and the Gcn2

protein kinase, which phosphorylates eIF2 and inhibits protein synthesis, has been shown to affect the expression of many proteins with negative effects on memory in Gcn2(-/-) mice. CPEB proteins control the translation of mRNAs by binding to the U-rich CPE region located in the 3'UTR.[68-70] Prion-like CPEB protein clusters are considered to be the default substrates for long-term memory, and CPEB3 is regarded as crucial for long-term memory and long-term synaptic plasticity in the hippocampus.[71,72] Additionally, Reselammal et al.[73] in their study emphasize that the prion-based mechanism of the CPEB3 molecule is important for long-term memory, supporting this notion. In a study conducted by Kozlov et al.[69] on *Drosophila*, it was observed that the deletion of the 3'UTR of the *Drosophila* CPEB protein Orb2 gene resulted in long-term memory loss.

Additionally, one of the most affected and studied regions in prion diseases is the hippocampus, which is responsible for memory and reinforcement.[74] According to a study by Ford et al.,[75] cognition and memory are among the six most problematic symptoms for caregivers of individuals with prion diseases. However, Joseph Stephan, who works on the prion-like protein CPEB3 in long-term memory, has stated that while the CPEB3 protein is indeed very important, it is not entirely sufficient for long-term memory.[72,76]

In conclusion, although prion proteins are widely known for their association with prion diseases, their cellular roles are quite diverse. Prion proteins, due to their flexible regions, are capable of self-conformational changes, making them proteins that essentially carry their own information. Prion-like proteins with similar domains can also undergo similar transformations. Their disadvantages include the potential to transform into pathological forms and exhibit a tendency to aggregate, while their advantages lie in their ability to contribute to memory formation. The cognitive impairments, primarily memory loss or decline, caused by prion diseases and prion-like protein disorders highlight the role of prion proteins in supporting memory and memory formation. However, further studies are needed to clarify the physiological and pathological roles of prion proteins.

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