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Research Article

System Prion Heterogeneity as Molecular Basis for Shifts in Conformer/Template Self-Amplification and Auto-Catalysis in Prion Diseases

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Abstract

The self-promotional traits of propagation, amplification and aggregation of para-prion proteins in the creation of protease-resistant isoforms that are unstable would include inherently contrasting molecular profiles of both homologous and heterogeneous moieties in a manner strictly arising from instability and deforming dimensions of a series of conforming templates. The PrPsc hence is an evolutionary end-product of promiscuous self-catalysis of the abundant normal PrPc cellular isoform that is widely distributed in cells throughout the body. The neuronal phenotype is an essential and crucial determinant of such shifts in conformer templating that in turn induces the participation of serial aggregation steps characterizing amyloid para-prion auto-catalysis. Significant involved dynamics of conformational shifts are inherent manifestations of heterogeneity within the molecular templating systems of self-generation and propagation of PrPsc species.

Introduction

Conformational instability of prion molecules is a targeted mechanism that underlies the dynamics and evolutionary course of para-prion-induced cell pathology. The crucial relationship between misfolded prion and neurotoxicity is currently unknown but may implicate dysfunctionality of the ubiquitin-proteasome system [1]. PrPc forms a substrate for conversion to abnormal PrPsc [2]. The essential molecular turnover of such mechanism occurs particularly within neurons of the central nervous system and hence with preferential involvement of non-dividing post-mitotic cells whereby clearance of the prion molecules cannot invoke cell division. Significant involved dynamics of conformational shifts are inherent manifestations of heterogeneity within the molecular templating systems of self-generation and propagation of PrPsc species. Strict conformer dynamics derived from templating has traditionally been considered a basic system series of pathways in the faithful replication of prions within neurons.

Conformer dynamics

Sialylation of N-linked glycans creates a prion replication barrier and hence affects replication rate and glycoform ratios [3]. PrP variant involvement in prions of heterozygous carriers is critical in understanding prion pathobiology [4].

Such a concept has now been modified in terms of possible 'deforming templating' in terms of the possible emergence of a whole array of homologous molecular entities in such disease progression. Beta-sheet-like formation may develop during mechanical unfolding of prion protein as revealed by single molecule experiments and simulations [5]. Indeed, the emergence of homology of molecular species appears an integral characteristic of the entire propagation cycle of para-prions that strictly self-determine the propagation and self-amplification of these 'infectious proteinaceous particles'. PrP may contribute to morphogenetic reprogramming of cells underlying epithelial-to-mesenchymal transitions and in fact regulates polysialylation of Neural Cell Adhesion Molecule 1 [6]. The conformational homologues are constitutive determinants that determine self-catalysis of the prion molecules that progress in evolutionary manner from the normal cellular isoform of the prion molecule. Considerably different PrP assemblies are observed in early-stage aggregates of PrP formed at low concentration on mica and Au surfaces in acetate buffer [7].

Self-amplification constitutes a series of adaptive changes as well-demonstrated by 'species resistance' pathways in ongoing transmission of para-prions from animal species to other different species. Protein misfolding develops by slow diffusion across multiple barriers in a rough energy landscape [8]. Aggregation of molecules seems an integral component pathway with conformational alterations that invoke transformation of the PrPc that is rich in alpha-helices to the PrPsc which is of beta-amyloid configuration. PrPc-organized multicomplexes have become recognized as candidates for anti-tumor therapy, since they function as scaffold proteins on the plasma membrane and these elicit distinct signaling pathways [9].

Amyloid beta-spine

The amyloid beta-spine of the amyloid fibril is a critical determinant in molecular propagation and allows also the development of hybrid fibrils from different species as described in the host organism. Prion strains are different self-propagating conformers of the same infectious protein [10]. It is the self-amplification of the amyloid fibrils that permits an array of homologues to be developed within regions of such molecules.

There has developed great interest in identification of compound that binds to PrPc, thus stabilizing its native fold and so act as pharmacologic chaperones to block prion propagation and

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pathogenic effects [11].

Interestingly, such a process of molecular propagation inherently allows the emergence of conformational plasticity that would account for new particle re-creation. Lack of the glycosylphosphatidylinositol anchor on prions may produce pose an increased risk for cross-species infection [12]. Systems of conformational change of molecules are therefore seen as a basic pathogenic series of transformations that require initially a prolonged incubation period in inter-species transfer. Propagated protein misfolding properties in both mutant and wild-type SOD1 and also TDP-43 may provide a molecular basis for contiguous spread of the amyotrophic lateral sclerosis through the neuroaxis [13].

Infectious traits

The infectious nature of prions is considered as other systems of transfer that include spontaneous (sporadic) generation of PrPsc and of hereditary forms of the various disease entities included within the general category of prion diseases. Prion diseases may serve as prototype of neurodegenerative disease, including Alzheimer disease [14]. It is further to such sequential and conformational systems that para-prion molecules further include propagation and spread between cells within a given species and between various species.

Fundamental concepts of self-determination are an inherent consequential basis for the evolution of the beta-amyloid molecular conformation. Several misfolded proteins may transmit disease pathogenesis in a prion-like manner by conferring conformational properties to normally folded molecules [15]. Systems of propagation in the laboratory based on protein misfolding complex propagation and on recombinant prion proteins would mimic the evolutionary course of PrPsc mechanisms of conformational plasticity and self-propagation, amplification and aggregation within pathologic lesions in animals and, presumably, also in humans. Assembly of amyloid proteins involves ordered arrangement of monomers as oligomers and in fibrils; this is accompanied by structural transitions with the formation of ordered beta- motifs in proteins and peptides lacking secondary structures [16].

PRNP gene

The PRNP gene responsible for production of PrPc is recognized as a target for some 20 possible mutational changes (point-mutations and truncations) that are associated with changes in the cellular prion molecules and as such may account for some hereditary aspects of prion molecular transfer. The application of mutational scanning and deep sequencing provides residue-level resolution of positions in the protein-protein interaction interface crucial to binding, and also quantitative measure of mutational impact on binding affinity [17].

Further to developmental aspects of a whole series of homologies, the molecular configurational change invokes additional propagation of self-amplification that increases beyond possible clearance mechanisms of prion molecules within neurons. Amyloid beta42 oligomers interact with PrPc as small oligomers (dimers and trimers) [18].

Structural conformers

Structural templates that strictly specify conformational identities to individual para-prion molecules inherently incorporate shifts in distribution of isoform homologous attributes as determined by the tertiary and quaternary structures of the para-prion molecules. Nucleic acid can catalyze conversion of alpha-helical PrPc to beta-sheet-rich proteinase K resistant prion protein oligomers and amyloid polymers both in solution and in vitro [19]. It is further to such distributional disarray that 'infectious proteinaceous molecules' can be generated and, in turn, capable of mutations and amplifications. The absence of nucleic acid within the para-prion molecule would account for the emergence of a huge array of conformational possibilities in molecular biology of prions. PrPc interacts physically with metabotropic glutamate receptor 5 and may be triggered by binding with soluble amyloid-beta oligomers [20].

Adaptation in shift transfer of prion configuration thus helps account for amyloid-beta dimensions in prion propagation that may also be applicable to other amyloid species such as the beta-amyloid in Alzheimer disease and other non-prion neurodegenerative states. Amyloid filaments transferred to a new cell may seed the conversion of PrPc to the same amyloid form, affecting cell phenotype [21]. Inclusive dynamics are invoked as a basis for homologous molecular species auto-catalysis that specifies the aggregation phenomenon per se. Distributional amplification may permit initial seeding of minute amounts of PrPsc in further generation of conformational change of the para-prion molecule. Neuronal GPI-anchored PrPc can serve in cell signaling implicated in survival and synaptic plasticity of neurons; amyloid-beta deviates PrPc-mediated signaling inducing toxic events [22]. Stacking of flat moieties, hydrogen bonding and molecular shape and electrostatic complementarities are implicated in interactions between R12 (a ribonucleic acid aptamer) and P16 (a partial peptide of a prion protein) and water-entropy gain by geometric characteristics of the biomolecules [23].

However, such seeding of PrPsc appears not an essential step in the creation and propagation of prions that accumulate in pathologic tissues, as indicated in particular by experiments utilizing recombinant PrP.

Shifts in templating

Conformer shifts come to play a distributional mechanism based especially on the amplification of sequences and side-chains built on the beta-amyloid spine of the PrPsc. Localization of PrPsc in specific brain areas is not understood [24]. Molecular Zipper constraints and molecular adaptation in the creation of homologous molecular species allow for determination of evolutionary traits in the configuration setting of PrPsc species. Lowering PrPc concomitantly reduces PrPsc in mouse brains inoculated with prions [25].

In a basic scheme of self-determination, the emergence of a whole series of homologous molecular species is further propagated as an adaptive series of transforming changes in the conforming template itself. Truncated prion protein molecules are found in brains of patients with some forms of transmissible spongiform encephalopathy [26]. The intrinsic mechanisms of self-propagation of PrPsc probably include the essential participation of other host moieties such as RNA and lipid chaparones that allow the free aggregation of a host of potential molecular species to the amyloid beta-spine.

Dynamics in self-determination

Determinants of dynamics of conformation change are crucial and self-amplifying in their own right and would permit the propagation

of PrPsc prion molecules in a series of further promotional systems of amplification that closely mimic an infectious transfer of protein molecules. Mass spectrometry has shown that both PrPc and PrPsc possess identical amino acid sequences, one disulfide bond, a GPI anchor, asparagine-linked sugar antennae, and unoxidized methionines and also the quaternary structure of the PrPsc multimer [27]. It is significant that the multiple possible alternative configurations are rendered possible by growth and amplification of the amyloid beta-spine in such a process.

Further significant accounts of distributional pathologic lesions are highlighted by the laboratory experiments in mouse, Syrian hamsters and cell lines utilizing protein mis-folding complex propagation and recombinant prion particles. A basic heterogeneity is operative in molecular and fibril growth of the amyloid moiety that can incorporate multi-species para-prions within systems of molecular plasticity and 'adaptation'. A key, hydrophobic domain within the prion protein, comprising residues 109-122 recapitulates helix-to-sheet structural transition, formation of fibrils and cytotoxicity of the misfolded isoform; stabilization of beta-hairpin structure around specific glycine residues of the peptide may enhance cellular toxicity by altering balance between oligomeric and fibrillar protein assemblies [28].

Prion biology

Para-Prion biology constitutes a revolutionary series of mechanistic pathways that cannot be accounted for by present concepts of molecular biology. Such mechanistic pathways include the auto-catalysis of molecular species in a serial propagation that can account for various forms of prion disease that include sporadic, infectious and hereditary transfer within human cells. The performance of configurational templating is considered crucial to the creation of a whole series of both homologous and heterogeneous molecular species that propagate the amyloid prion particle. PrPc plays a critical role in neuronal differentiation of neural stem precursor cells and this function appears dependent on neural cell adhesion molecule [29].

Promiscuous conformational change is intrinsically linked to quantitative aspects in molecular stability. This is important in the exposure of various moiety side chains or epitopes that are further determining functionalities in amyloid self-amplification. The further conformational disarray is thus itself further mechanistic enhancer in conformer shifts in molecular templating.

Host co-factors

Host factors, as copolymers in amyloid self-amplification, are invoked as platform determinants in the evolutionary creation of both amyloid particles and of the conformer templates. Such processes operate in the creation of self-amplifying and self-propagating prion particles that are based on essential aggregation dynamics of component molecules.

Performance dynamics can be viewed as strict determinants in homologue and heterogeneous participants in system pathway plasticity based on further aggregation dynamics of molecules within individual neurons. The cell-to-cell transfer of PrPsc combines the dynamics of auto-catalysis with the inherent aggregation of amyloid particles as fibrils of variable conformation.

Concluding Remarks and Summary

Para-Prion biology constitutes a revolutionary series of mechanistic pathways that cannot be accounted for by present concepts of molecular biology. Aggregation of molecules appears a series of integral component pathways in conformational alterations that invoke transformation of the PrPc, which is rich in alpha-helices. The resultant PrPsc is of beta-amyloid configuration. Performance dynamics are crucial self-determinants in strict conformation of molecules arising from both homologous and heterogeneous participants in amyloid/template auto-catalysis. The distributional patterns of misfolded molecular species are an essential, inherent system of self-promotion. The cell-to-cell transfer of PrPsc combines the dynamics of auto-catalysis with the inherent aggregation of amyloid particles as fibrils of variable conformation.

As such, there develops a series of side-chain and hydrogen bonding phenomena that entail epitope exposure and conformational specification by molecular constraints of the amyloid beta-spine. It is further to such contrasting constraints and promiscuous permissiveness that para-prion self-propagation is enacted within the molecular confines of individual neurons and between networks of individual neurons. It is significant to view the dimensional scope of conformer/templates as generating systems for such contrasting homologous and heterogeneous molecular conformational disarray.

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