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PRION-DEPENDENT PHENOTYPIC HEREDITY: A VIOLATION OF CENTRAL DOGMA THEORY AND LAMARCKIAN INHERITANCE

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ABSTRACT

Misfolded proteins which have the ability to pass on their misfolded form to regular variants of the same protein are defined as Prions. They are associated with a number of lethal and transmissible neurodegenerative diseases in humans and many other species. The two-step process by which information in genes is converted into proteins is explained by the fundamental dogma of molecular biology. Similarly, Lamarckian inheritance claims that an organism has the ability to pass on physical characteristics acquired by the parent organism to its offspring during its lifetime. There is an exception or limitation to these theories. The genetic properties incorporated in prions established the causes of central Dogma theory violation, this occurrence appears to be a distinctive phenomenon and consequently stimulating a genetic mutation as the case may be. This critical review attempt to provide an insight to factual existence of Prions, Definitions, Functions, hypothesis of misfolded proteins, why Central Dogma theory (CDT) need to be revisit, Limitations to CDT, Factors responsible for limitations and challenges.

KEYWORDS: Prion, protein, infectious disease, review.

1. INTRODUCTION

The discovery that genetic information is preserved in DNA as a coded series was a significant development in biology. Watson and Crick's observation is as significant, unfalsifiable, as Darwin's theory of evolution.[1] The entire method, from Darwin to Mendel, Avery, Watson and Crick, was a scientific breakthrough that gave rise to molecular biology as a modern unique discipline. Molecular biology now stands on an immense body of experimental genetic data with a promising future, this fantastic achievements over the last six decades are mainly attributable to two things: a fundamental theory to understand how knowledge is stored; and comparative analysis of this gene.[2,3] However, a compact group of biologists have uncovered some alarming incongruities that may challenge this central hypothesis. Similarly, our curiosity lies within this concern: is the Central Dogma of molecular biology which opined that “all genetic material is processed and distributed digitally by DNA” the only plausible interpretation of how life has/can evolve, or are there other techniques of heredity in living organisms? As a matter of fact, there are growing evidence that genetic information can also be transmitted analogously in prions.

Prions are misfolded proteins capable of transferring their misfolded form to regular forms of the same protein. They are defined as serious, with infectious neurodegenerative diseases in humans and a variety of other animals.[4] The major factor causing normal protein to misfold is yet to be known, however, an irregular three-dimensional structure in prions is accused of conferring infectious properties, breaking down the surrounding protein molecules into similar structures. Based on the central dogma theory of information flow, the term prion derives from "proteinaceous infectious particle," which denotes the role of a protein as an infectious agent, negating all other known infectious agents such as fungi, bacteria, viruses, and parasites, all of which have a constituent of nucleic acids (DNA, RNA, or both).[5,6]

The central dogma theory was proposed by Francis Crick in 1956.[1] According to the theory, once "information" has been transmitted into protein, it cannot be retrieved. Furthermore, information can also be transferred from nucleic acid to nucleic acid or from nucleic acid to protein, however, it cannot be transferred from protein to protein or from protein to nucleic acid. This means that chromosomal DNA acts as a template for synthesis of RNA that moves to cytoplasm and encodes the amino acid sequence of the proteins. According to Figure 1. A description of information flow from DNA to RNA and RNA to proteins is established. Similarly, reverse transcriptase allows information to travel back from RNA to DNA, yet, there is no information transfer from protein to nucleic acid, however, prions proteins convey information from protein to protein in a self-replicating manner, thereby violating the Central Dogma postulates. All embedded in these steps are: Replication, Transcription and Translation.[7,8,9,10] The Replication is defined as the process of synthesis of DNA from DNA via DNA polymerase, similarly, transcription is the process of synthesis of RNA from DNA via RNA polymerase. While Translation is the process of synthesis of proteins from mRNA within the Ribosomes. However, it is important to note that there is no flow of information transfer back from protein to protein or protein to Ribonucleic acid, this formed the basis for prions exception.

A schematic representation of cellular prion protein (PrPC) is shown in Figure 2. PrPC's N-terminal domain is unstructured and contains distinct sequences known as octapeptide repeats. These octarepeat regions have hystidine residues (in blue) that can bind monovalent and divalent cations like copper ions Cu+ and Cu2+ (orange dots). At the C-terminus, there is a single disulphide bridge (in red) and two glycosylation sites. Green coloration represents the asparagine residues implicated in protein glycosylation. The cumulative arrangement of the C-terminus is made up of two short antiparallel beta sheet strands (β 1 and 2) and three α helices (1, 2, and 3). A third β sheet strand has recently been discovered and labeled as β0 in yellow.[11]

Crick proposed three other hypotheses to best explain Central Dogma theory, these include: (i) Sequence hypothesis, (ii) Adaptor hypothesis and (iii) Hypothesis regarding protein folding. According to the sequence hypothesis, the specificity of a nucleic acid is dictated by the nucleotide sequence, which in turn encodes for an amino acid sequence of a certain protein. The adaptor hypothesis explained the incorporation of hydrophobic amino acids in proteins that will not interact with hydrophilic nitrogenous bases in RNA. The hypothesis regarding protein folding states that the amino acid sequence solely determines the protein folding.[10,12,13,14]

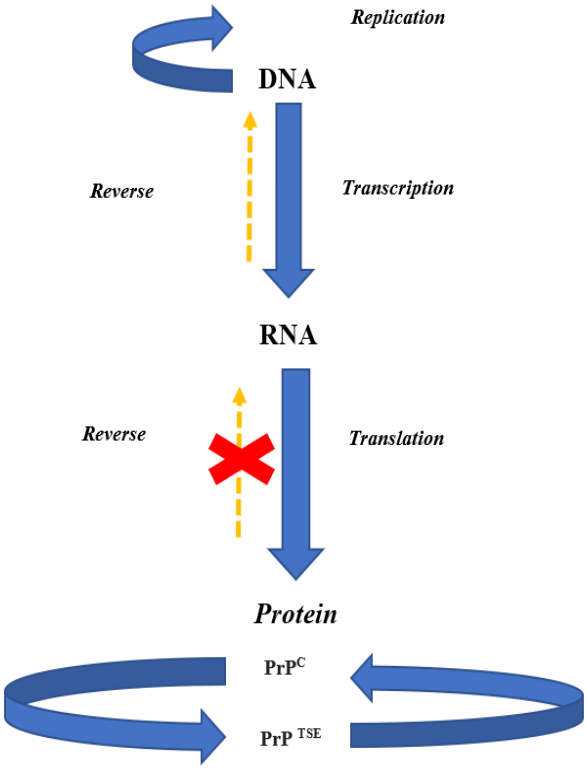

Figure -1: This figure depicts a violation of central dogma theory indicating flow of information within different macromolecules: Deoxyribonucleic acid (DNA), Ribonucleic acid (RNA), cellular prion protein (PrPC), misfolded isoform of the prion-protein (PrP^{TSE}), transmissible spongiform encephalopathy (TSE).

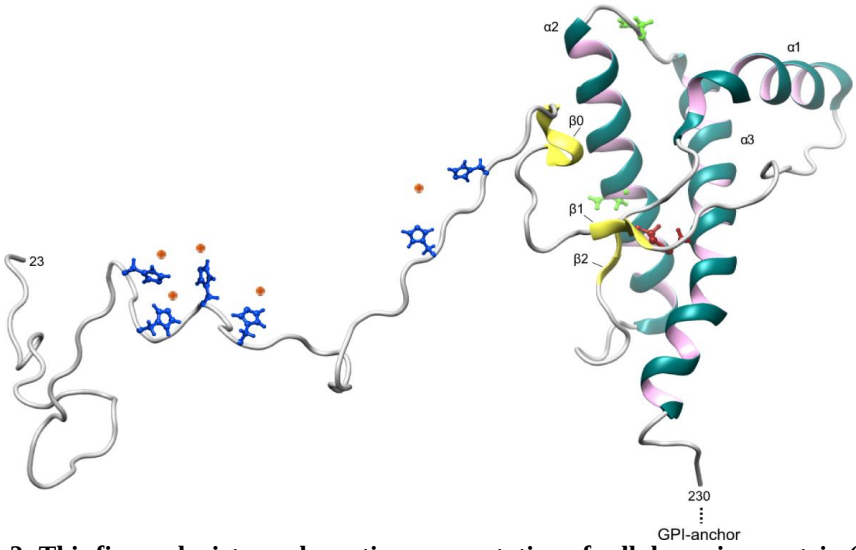

Figure 2: This figure depicts a schematic representation of cellular prion protein (PrP^C).

Source: Legname (2017)

1.1 Limitations and challenges to Central Dogma theory with implications to Lamarckian inheritance theory

The Lamarckian inheritance theory states that an organism will pass on to its descendants the various traits that it gained during its lifespan. It is proposed that the different modifications that occur in an organism's body in order for it to respond to changes in its environment will be carried on to its offspring. Apart from Darwin's popular principle of natural selection, the Lamarckian inheritance of genetic predispositions has been used to describe the natural mechanism of species evolution. The Central Dogma is often associated with the alleged variation in Lamarckian inheritance.[2] Indeed, if information transfer from proteins to the genome occurred, environmental influences might be expected to have a guided impact on genomes. A closer analysis of the available evidence, however, reveals that violation of the Central Dogma is not required for Lamarckian evolution, and that not all evolutionary phenomena involving such violation are actually Lamarckian. Main exceptions to the central dogma theory are discuss bellow**:**

(a) Discovery of reverse transcriptase*:* Temin Howard and Baltimore David was able to established reverse transcriptase in retroviruses (then RNA tumor viruses) in 1970,[15] which changed the course of molecular biology and set the way for retrovirology and cancer biology.[16] The central dogma theory of molecular biology explained the sequential transfer of information from DNA to RNA and then to Protein (DNA → RNA → protein pathway). Similarly, it also explained that such information cannot be conveyed from a protein to a nucleic acid or vice versa. Reverse transcriptase (RT) is a DNA polymerase enzyme that converts single-stranded RNA into DNA, therefore defying the central dogma idea. It's also referred to as RNA-dependent DNA polymerase. This enzyme can generate double helix DNA after reverse transcription into single-strand DNA in the initial phase.[17]

(b) Formation of prions*:* Prions are proteinaceous infectious particles that lack nucleic acids either DNA or RNA and are made up exclusively of proteins. The prions are capable of transferring the information to normal protein to fold abnormally resulting in various transmissible encephalopathies like kuru, scrapie etc.[18] Prions-mediated inheritance can be transformed into prion-independent genomic inheritance when supplemented with genetic variation. The most recent screening suggests that prions are widespread in fungi, thus, establishing the transfer of information from proteins to the genome, directly contradicting the Central Dogma of molecular biology.[19,20]

(c) The role of chaperons in protein folding*:* Watson and Crick proposed that the amino acid sequence determine the protein folding.[1] However, chaperons also known as molecular chaperones are the proteins that facilitate protein folding, chaperons are only involved in preventing misfolding and providing conditions favorable for folding. Chaperones could aid in the transformation of a prion from its native to infectious state.[21] Several scholars have suggested that the normal operation of the cellular chaperone mechanism, or its dysfunction in certain situations, may contribute to the emergence of prion diseases. Most of these theories are focused on the observation that such chaperones are capable of fixing a protein chain's partly unfolded state, which may theoretically promote the transfer of a prion from its natural form to amyloid.[22,23]

(d) Epigenetics modification of DNA and chromatin: Epigenetics modification became rooted in RNA interference, RNA splicing and RNA editing, mature mRNA is formed through extensive spicing, editing etc. chromatin also undergoes modifications like methylation, phosphorylation, acetylation etc. The demonstration that prions occur not only in animals but

also in yeast through epigenetic inheritance of phenotypic traits, was a landmark finding that significantly facilitated further research of prions.[2,24] The prion proteins have two distinct conformations: one that is soluble and the other that aggregates to form amyloid-like fibrils. The amyloid-forming conformer is self-replicating: when a prion molecule adopts this conformation, it interacts with other molecules in the soluble conformation, causing them to convert to the amyloid-forming conformation as well. Thus, prions are analog heredity agents, as opposed to the more common nucleic acid-mediated digital heredity.[3,25,26]

1.2 Evolution, Structures and Mechanism of prion proteins

Following the discovery of double helix structure of DNA (deoxyribonucleic acid) by F. Crick and J. Watson in 1953.[1] DNA is replicated by polymerases that take instructions from templates and is made up of four types of bases coupled to a sugar-phosphate backbone. A pair of nucleic acid chains with complimentary sequences can form a double-helical structure. The transfer of DNA information into functional molecules via protein synthesis is known as gene expression. Abnormal structured proteins are known as Prions. Prions are misfolded versions of standard cell proteins with a distinctive tendency to transform their naturally folded counterparts to further prions. The investigation of critical molecular processes involved in prion misfolding may also aid in the prevention of protein misfolding disorders. The basic molecular mechanisms that lead to the conformational transition remain unknown. However, according to the 'protein-only' theory, PrPC is capable of undergoing conformational transformation into an insoluble isoform known as PrPSc ('Sc' for 'scrapie') which is considered to be the agent that causes transmissible spongiform encephalopathies (TSEs). Several experiments have tried to investigate the pathways involved.[2,3,24,25]

Jogender Singh and Jayant Udgaonkar of the National Center for Biological Sciences (NCBS, Bangalore) gave a partial insight to this issue.[27] Their findings on the prion protein established that certain genetic mutations can altered the shape of the proteins via deformation leading to an irregular 3-D configuration of the prion. The researchers used one of the first prion proteins, simply known as "Prion Protein" (PrP), as a model to investigate how naturally occurring amino acid mutations could disturb the normal protein structure, causing it to misfold.[27,28] The processes begin with the PrP component named "5-007-helix 1" – a helix shaped structure. Sequel to the destabilization of this structure and the adjacent loop due to pathogenic mutations, structural misfolding is facilitated in other parts of the prion protein and the rate of normal-to-prion conversion of PrP is increased. The disorder induces the development of flat sheet-like structures that contribute to the transformation of other protein helices into sheets. Their investigations established that the misfolding degree in the mutant PrP was strongly correlated with the extent of destabilization induced by the mutation in the α-helix 1 region.[27,28,29] Subsequently, the misfolded proteins therefore join together to form spherical oligomers, the subunits of which are misfolded prions. When these protein oligomers become accumulated in nerve cells, they are responsible for primary cause of neurodegenerative complications and eventually mortality in patients with prion diseases.[27]

Similarly, another investigation by Kupfer et al.[30] reported that Spontaneous protein misfolding may occur more frequently under physiological conditions that are commonly expected. The authors argued that Chaperones may play a key role in the prevention of pathogenic effects of misfolding and aggregation. The extracellular chaperone clustering is one of the most interesting examples, which prevent the production of amyloid in human lysozyme.[31]

Furthermore, subsequent study by Yin et al.,[32] showed that recombinant PrP with various pathogenic mutations had a wide vulnerable amino terminus and more closely attached to glycosaminoglycans. As core elements of amyloid glycosaminoglycans are present in PrPSc in vivo, it has been shown that they promote the transfer of PrPC to PrPSc in vitro as well as PrP-aggregation.[30,33] Lipids and nucleic acids also bind to PrPC and are observable in PrPSc-aggregates; additionally, they can promote PrP-conversion by serving as a scaffold that attaches and concentrates PrPC in order to provide high quantities of substrate for conversion to PrPSc.[34]

1.3 Incidence, prevalence and Epidemiology of prions disease

Prion diseases often known as transmissible spongiform encephalopathies (TSEs) are a group of rare progressive neurodegenerative disorders that affect both humans and animals. They are characterized by long incubation times and distinctive spongiform modifications which are consistent with neuronal loss and inability to cause inflammatory reactions. The causative agents of TSEs are considered to be prions.[18] The irregular folding of the prion proteins contributes to brain injury and to the hallmark signs and symptoms of the condition. Prion diseases are typically quickly progressive and often terminal. This misfolding process can be sporadic, similarly to a genetic mutation, or stimulated as a result of pathogenic prions absorption. Examples of Human diseases caused by prions include: Variant Creutzfeldt-Jakob Disease (vCJD), Creutzfeldt-Jakob Disease (CJD), Gerstmann-Straussler-Scheinker Syndrome, Fatal Familial Insomnia and Kuru while animal diseases caused by prions are: Chronic Wasting Disease (CWD), Bovine Spongiform Encephalopathy (BSE), Scrapie, Feline spongiform encephalopathy, Transmissible mink encephalopathy, Ungulate spongiform encephalopathy.[35,36,37,38]

The most prevalent human prion disease (HPD) is Creutzfeldt-Jakob disease (CJD), with an age-adjusted occurrence of 1.2 cases per million persons per year in the United States, close to the incidence recorded in other nations.[39] Sporadic CJD responsible for about 85 per cent of CJD cases and 10 per cent to 15 per cent of family CJD cases, CJD variant (vCJD), was identified in the United Kingdom in 1996 and was discovered following the ingestion of prion-contaminated beef products via bovine spongiform encephalopathy (BSE).[40] Furthermore, some patients with vCJD were found to have contracted their disease after obtaining blood from donors that eventually acquired vCJD. By January 2020, 232 cases of vCJD have been recorded worldwide. Other less prevalent prion diseases include fatal family insomnia, intermittent fatal insomnia, Gerstmann-Straüssler-Scheinker syndrome, protease-sensitive prionopathy, and acquired prion disease.[41]

The CJD was first identified in the early 1920's. The primary variant of human prion diseases, subtype CJD, develops similarly in both sexes with a peak age between 60 and 69 years of age. The SCJD takes place all year long, with no seasonal variations.[4] General clinical symptoms include progressive dementia, followed by impaired vision and cerebellum functioning disorders, myoclonia, pyramidal and extrapyramidal dysfunction, or akinetic mutism. The length of the events in the SCJD is comparatively limited.[4,42] The median recovery time for Chinese sCJD cases is 7.1 months (range: 1.0–23.3) and 78.5 percent of patients die within one year of onset.

These data are similar to those of Western countries, but vary from those of Japan.[43,44] A research performed by the European CJD Surveillance Network (EuroCJD) involving 2,451 patients with sCJD found that the median survival period was five months with 85.8% mortality within a year. Also, in Argentina, the median period of sCJD disease is 4.6 months. By contrast, the study conducted by the Japanese CJD monitoring program found slightly longer durations of disease in Japanese patients with prion diseases (most of them with a subtype of sCJD), with the mean period 17.4 months in 855 patients and just 46.0% mortality within one year.[4,45]

An international documentation on the epidemiological manifestations of sCJD examined 3,720 cases of sCJD in nine European countries, along with Australia and Canada, it was observed that the average annual sCJD mortality rate is 1.39 per million.[46] In Japan, age-adjusted mortality rates rose from 1979 to 2004 with an average mortality rate of 1.48 per million in 2004.[47] The Chinese CJD monitoring network posted an annual CJD morbidity rate of 0.91 per million in Beijing.[4]

Comparative analysis from all countries through the CJD International Surveillance Network (1993 to 2013) revealed that mortality has an increased rates (millions) per annum.[39] The case was also similar to that of United states.[48] However, it is important to note that the most CJD cases from these data were European Americans (94.6 %) which is 2.7 times higher than that of African Americans. Justification for these variations are yet to be established.[49]

2. Biological and Physiological Functions of the Cellular Prion Protein

Cellular prion proteins (PrPC's) have been attributed to several Biological and Physiological functions, however, cell signaling is one of its most incredibly interesting functions. Along with its extracellular location, the protein has the ability to transmit environmental molecular signals to the cell.[11] Since PrPC is glycosylphosphatidylinositol (GPI)-anchored to the cellular membrane and lacks direct access to the cytosol, signal transduction cannot be mediated directly by PrPC and consequently stimulating an interaction with other transmembrane proteins.[50]

The identification of a caveolin-1-dependent associated with PrPC in the proto-oncogene tyrosine-protein kinase Fyn is perhaps the most significant study and the first proof that PrPC may be involved in mediating extracellular signals.[51] After this pioneering work, it has become clear that PrPC can act by collaborating with other membrane proteins to transmit cellular signaling. One preferential PrPC interactor was known as the neural cell adhesion molecule (NCAM). PrPC can promote neuritogenesis through the tyrosine kinase Fyn by physically interacting with NCAM.[52,53] A soluble phase of full-length PrPC, in particular, has been used for focal stimulation of neurite outgrowth and guidance.[54]

Furthermore, it has been demonstrated in another study that PrPC is important for NCAM-dependent neuronal differentiation of neural stem/precursor cells.[55] PrPC is a developmentally regulated protein, and its high expression in the developing brain may be important in controlling neurogenesis and cell proliferation [56]. According to a recent study, PrPC plays an important role in regulating synaptic plasticity in the developing hippocampus through protein kinase A (PKA), thus promoting proper synaptic development in adulthood. Myelin formation and maintenance is an essential feature associated with PrPC expression. Aging PrP knockout mice exhibit a distinct phenotype of demyelinating disease in the peripheral nervous system. Molecular research has shown that the N-terminus of PrPC interacts as a disputative ligand of the adhesion G-protein coupled receptor G6 (Adgrg6) receptor, whose role is essential for myelin maintenance.[57,58]

1. Final Conclusion and prospects for the future

Prions are analog, protein conformation-based inheritance agents that can confer beneficial phenotypes to cells, especially when stressed. Prions-mediated inheritance can be channeled into prion-independent genomic inheritance when combined with genetic variation. Because of its central function in a cluster of

neurodegenerative disorders known as prion diseases, the prion protein (PrP) has been extensively studied. In modern cells, there is a non-negligible flow of information from proteins to the genome, directly contradicting the Central Dogma of molecular biology and Lamarckian inheritance theory. Therefore, evidence suggest that there is a violation of Central Dogma theory and Lamarckian inheritance in Prion-dependent phenotypic heredity. As explained earlier in this paper, several functions of PrPC have been established in recent years. The use of PrP knockout mouse models has established the molecular pathways in which the protein is involved. However, it is important to bear possible bias in these responses, by studying the physiological function(s) of PrPC with current state of the art bioinformatics tool for structural simulation, prediction and diagnosis. With this, we should be able to advance our understanding of the neuropathological processes underlying prion diseases and establish novel therapeutic approaches to such devastating disorders.

Disclosure and conflict of interest

The authors declare that they have no conflicts of interest.

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