SYSTEMATIC REVIEW

A Theoretical Framework on the Biology of Prion Diseases

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ABSTRACT

Background: Prion diseases or TSE diseases are a group of neurodegenerative disorders that manifest in several forms in humans, such as Kuru disease, Creutzfeldt Jakob disease (CJD), Gerstmann-Sträussler-Scheinker syndrome (GSS) and fatal familial insomnia. **Objective:** In this study, we propose a multimodular hypothesis of prion diseases. According to this hypothesis, a prion disease manifests because of the interaction of two genetic modules, such as the PRNP gene module and that of the gene or genes responsible for one or more chaperones, with one or some chemical module on whose structure the products of the genes or genetic modules interact. **Methods:** This study presents the perspective that modular thinking can allow us to overcome conceptual obstacles in the understanding and interpretation of prion diseases. **Results and Discussion:** The structure of the chemical module or modules is directly responsible for the folding or misfolding of the PrP^{C} protein. The etiology of acquired prion diseases is explained based on this hypothesis. Hence, it has been proposed that (g) CJD involves the PRNP gene mutant and one or more mutant genes for one or more chaperone genes. In contrast, sCJD has one or more mutant chaperone genes. When does iCJD occur? Healthy individuals manifest acquired prion disease through contamination when infected with one or more mutant chaperones. The mutant chaperones interact with the prion protein, and PrP^{C} is converted to its isoform PrP^{Sc}. In a recent study, there was a case of an individual with CJD after COVID-19 infection. **Conclusion:** This case emphasizes the link between neuroinflammation and protein misfolding and provides proof that chemical module formation is a necessary condition for the manifestation of prion diseases.

Keywords: Prion, genetic module, chemical module, chaperone, modules.

1. BACKGROUND

In addition to "tree" thinking, which interprets phylogenetic relationships between taxa, and evolutionary or population thinking, modular thinking is also gaining traction (1). This type of thinking is based on the knowledge of modules as functional units by which living organisms secure their survival and reproduction (2). Almost two decades ago, the idea was proposed that there will be a transition from molecular biology to modular biology in the future (3). It is well known that science is a way of thinking before it is a body of knowledge (4). The idea of modules and modularity is not a new idea (5). It is a known fact that organisms are composed of parts, but as J. Michael states, there is not yet an answer to the question of what we mean by the structure and function relationship (6). In this study, the structure-function relationship refers to modules, which, like a coin, have two sides. G. Schlosser and G.P. Wagner analysed modules simultaneously from structural and functional perspectives (7). We will apply this mode of thinking to prion diseases.

Prion diseases or TSE diseases are a group of neurodegenerative disorders that manifest in several forms in humans, such as Kuru disease, Creutzfeldt-Jakob disease (CJD), Gerstmann-Sträussler-Scheinker syndrome (GSS) and fatal familial insomnia (8). Similar conditions are seen in animals, such as so-called natural scrapie in dogs

and goats, encephalopathy in N. vison (mammal of the mink family, Mustelidae), CWD in captive mule deer, mad cow disease or bovine spongiform encephalitis, and diseases in some species of exotic bovids and the domestic cat.[9]

2. OBJECTIVE

This study presents the perspective that modular thinking can allow us to overcome conceptual obstacles in the understanding and interpretation of prion diseases.

3. MATERIAL AND METHODS

The first conceptual obstacle is thinking of the gene as a genetic module. The structure of a genetic module, similar to any other module, is a set of molecules whose interaction is based on several forms of interaction information, such as chemical, genetic, and epigenetic information.

The second conceptual obstacle is related to the function of a chemical module, which is not conceptualized in nonmodular thinking because in today's thinking, the existence of other forms of information than genetic is not accepted.

Hence, our efforts regarding prion diseases address not only genetic but also chemical modules, and from this perspective, the multimodular hypothesis was formulated to understand and interpret the genetic, sporadic and acquired etiology of these diseases.

4. RESULTS AND DISCUSSION

Modules: general considerations

The definitions of modules vary according to the levels of life organization, which is probably the main reason they are so different.[10] Some scientists use graph theory to describe the molecular communities of genes, proteins and different metabolites.[11] Other scientists consider this molecular connectivity to be arbitrary and implausible.[12]

In this study, as mentioned above, we will focus on our understanding and interpretation of modules from two perspectives. From the structural perspective, modules can be sets of molecules, of macromolecules, of cell organelles and cells, of modules themselves, or of individuals of the same species and of different species. The interaction information between these compositional elements and the formation of the relevant effectors perform a particular function.

It is of great importance that when we discuss information as the basis for the structure of modules, genetic information is not the only information to consider. The DNA molecule is not the whole book of life but only a part of it.[13]

This study adopts the idea that information is material and concrete, that it is an attribute of matter that feeds evolution, that interactions are a result of information. [14] Also, we assume that information is a basic property of the universe and that evolution is the gain of information over time.[15]

Specifically, living organisms contain many forms of interaction information, such as chemical, genetic, neural, mixed, socio-cultural and linguistic information.[16] From the various forms of interaction information developed through self-organizing and selection processes, modules at different organization levels of life have been formed. These modules include chemical or biochemical, genetic, epigenetic, neural (simple, neuroendocrine and complex), organismic, species and ecosystem, mirror, sociocultural and linguistic modules.

Each type of module mentioned above appears in several forms. For example, mirror modules appear in some higher animals and in humans in the various gestures through which some nonverbal communication functions are performed.[16] From this perspective, it is clear that genetic modules are important, but they are not everything and are not completely dominant over other modules.[17]

All modules, when interacting with the internal and external environment, display a particular form of information. This information is called modular, functional, or semantic information, i.e., it has meaning. The value of semantic information is measured by the probability of the function being performed by an individual or by a population. The display of this function is analogous to how an intelligent agent performs its function.

Therefore, from a functional perspective, the module is an intelligent agent. Through its structure, a module "perceives" the object upon which it needs to act, which is a "lock" that needs to be opened, stores information about it, and based on this information, it forms an effector, which is the key that opens the lock that is, and it performs its particular function.

Based on this concept, modules can be analysed in terms of a reaction or action that they carry out, not only as a function that performs a task for the living organism but also as a process that occurs in organisms in an abnormal state when suffering from a certain disease.

Modules as structure and function in prion diseases

Prion diseases have drawn the attention of researchers because of their particular biological nature.

Up until 1982, when the Nobel Prize winner S. P. Prusiner coined the term "prion" for the infectious protein, it was accepted that genes perform a specific function via the proteins they form; or are abnormal and do not perform the proper function.[18]

The same thing happens even in the case of prions: from the cellular prion protein (PrPC), its isomorph is formed, called PrPSc, which turns into a fibrillary mass and multiplies and deposits in the human brain leading to its damage. This multiplication of the PrPSc protein has surprised the scientific opinion due to the fact that even today it is hard to conceive another form of information other than genetic information.

In fact, as mentioned above, living systems use chemical information, which is one of the forms of interactive information. Such a conceptual obstacle appeared when scientists encountered the transmission of this chemical information, which we call infection in analogy with microbes. In the last case, we are referring to the interaction among different proteins, such as PrPC, PrPSc and chaperones. It is known that the interaction between these molecules, because of the chemical information, is responsible for both correct folding and misfolding.

Everything stated above is related to the meaning and interpretation of modules from a structural perspective. To be better acquainted with the modules in prion diseases we compare them with genetic modules, starting from a functional perspective. The structure of a genetic module is formed as an intelligent agent, which, after depositing information about a task to be performed or a requirement to be completed, metaphorically called 'lock', forms according to this information an effector, which is a 'key' that opens the 'lock', i.e. performs

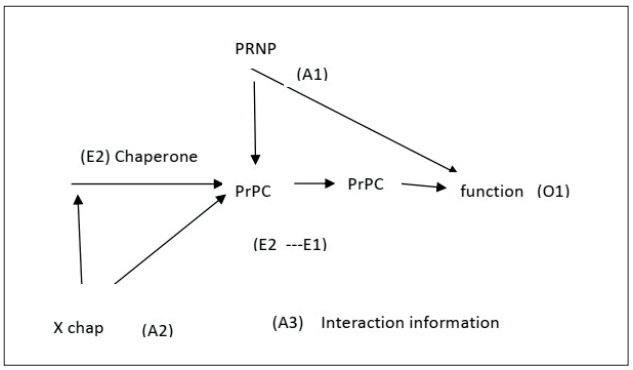

Figure 1. Multi modular interaction

the relevant function.

In the case of prion diseases, the structure of the module is formed as a chemical process that does not perform any function, but on the contrary, it brings about a disorder that might lead to the death of the living organism.

From the structure perspective, a genetic module is a set of molecules, elements of which interact with one another based on chemical and genetic information. Specifically, the chemical information acts, when referring to the ribosomal complex, for the binding of enzymes and proteins with DNA, for the binding of tRNA with its corresponding aminoacids, as the genetic information acts while referring to the genetic code. It should be noted that scores of chemical or biochemical modules form the structure of the genetic module. Hence, the structure of a genetic module is the entirety of chemical or biochemical modules and the name genetic, epigenetic, neural module etc. are given based on the function perspective of modules.

Modules as intelligent agent: multi modular interaction

As stated in a study the gene itself is considered a genetic module.[19] Said this, from the structure perspective a genetic module is a set of molecules, elements of which interact with one another based on chemical and genetic information. The information that DNA fragment contains has been extracted and deposited from the past, from a certain environment and it is able to recognise a request or to respond through its genetic product. According to us, the model proposed above needs to be modified.

It is known that the three-dimensional shape of protein structure is determined by the sequence of amino acids and the so-called protein enzymes, or molecular chaperones. The molecular chaperones accelerate the process of protein folding and without them the cell could not perform any of its functions, hence no cell could live.[20]

In *Figure 1* it is shown the interaction network of three modules: the genetic module of PRNP gene (A_1) with normal protein PrPC as an effector (E_1), the genetic module of XChap gene (A_2) with protein chaperone as an effector (E_2) and the chemical module with chemical information (A_3) which makes possible the interaction between the two effectors of genetical modules, namely, E_1 and E_2.

Genetic modules act as intelligent agents. An intelligent agent such as PRNP gene (A_1) or XChap gene (A_2), collect and deposit the information to carry out a task, metaphorically speaking, a lock to open (specifically, O_1 and O_2). Based on this information, the effectors such as PrPC (E_1) and chaperones (E_2) are formed, or the keys to open the respective locks mentioned above, to fulfil the task requested.

As in other cases, in prion diseases, PrPC performs its function in three-dimensional (3D) structure and to do this, the respective chaperones are requested. This means that XChap gene (A_2) must recognize the "lock" (O_2) according to which an effector will be formed (E_2). This is what happens: molecular chaperones assist nascent protein PrPC to reach their native fold. The functioning of chaperones can be impaired not only by their blocking by misfolded proteins, but also by post-translational modifications.[21]

However, chaperone "help" is not enough. The PrPC-chaperone connection or E_1-E_2 effectors connection does request the molecular recognition or the chemical information (A_3) of which a chemical module is formed. The chemical modules do not have effectors but any interaction associated with a particular function, is considered a module, meaning, a functional unit.

In other terms, we emphasize that in relation to the appearance of the normal function of PrPC, specific conditions must be met according not only to the normal genetical information of PRNP (A_1) and XChap (A_2) genes but also to the chemical information (A_3) of the environment in which effector E_1 and E_2 interact. Probably, the role of chemical information and chemical module is shown in the case of manifestation of prion disease from PrPC misfolding because of neuroinflammation.[22] More specifically, in the case above, it is impossible to explain the formation and reaction of the chemical module but the fact that mutations of PRNP and XChap genes are not stated, support our idea that misfolding is connected to the interaction of chemical information and the formation of a chemical module, or modules. Another chemical module is formed by the interaction of a native prion protein with an infectious form of the prion with an incorrect conformation.[23]

Thus, the development of neurodegenerative diseases of an amyloid nature is based on two processes: a change in the structure of an amyloidogenic protein and the formation of various aggregates from such a protein with a disturbed conformation.[21] In both cases a chemical module is formed.

Multi modular model of prion disease

In *Figures 2, 3* and *4* are shown three modular models, specifically for gCJD, sCJD and iCJD. Based on *Figure 1* it is easy to explain the genetic (*Figure 2*), sporadic (*Figure 3*) and acquired etiology (*Figure 4*) of prion disease. For example, in *Figure 4* it is shown that an individual can exhibit prion disease iCJD because it has been exposed from the mutant chaperones, which can act as "seeds" in the conversion from PrPC to PrPSc.

This is similar to the *Figure 3* where mutant chaperones make possible the manifestation of sCJD.

The low probability of simultaneous presence of mutant PRNP and XChap genes explains the low percentage of gCJD, from 10 to 15 % (*Figure 2*) and the high percentage of sCJD, approximately 85% (*Figure 3*). Another possible explanation is related to the nature of genes: mutations occur more often in XChap gene than in PRNP gene. In this case, the best explanation could be related to the chemical module because it directly affects the folding and misfolding of PrPC. Probably the chemical module plays the same role as when the environment affects the phenotypical appearance of a particular genotype.

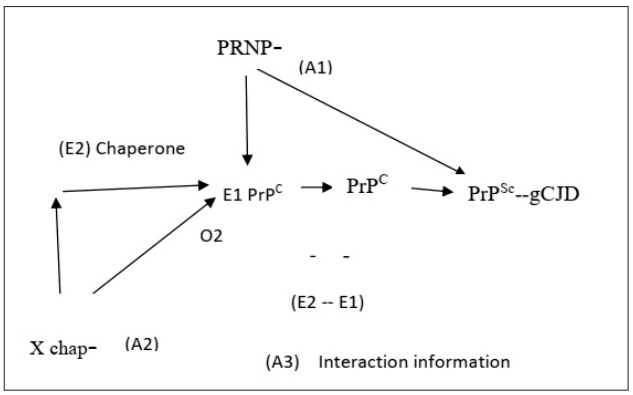

Figure 2. Multi modular model of gCJD

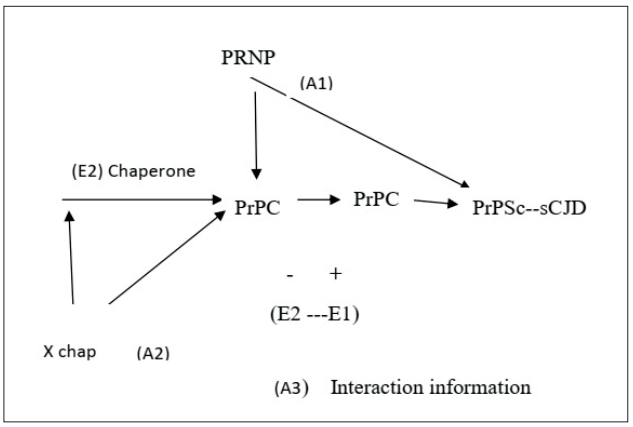

Figure 4. Multi modular model of iCJD

Like any gene product, even in the case of PRNP gene the prion protein is detected by a chaperone. Other authors have hypothesised, calling it the protein X, according to which, there is an unidentified cellular protein that by bonding PrPC and PrPSc proteins together, enables the conversion of PrPC protein to its isoform PrPSc.[24] We support this idea, but we believe that protein X is a molecular chaperone. The idea that the molecular chaperones induce a transformation of prion protein into similar aggregates with amyloid structures has also been given later.[25] The role of chaperones in the development of amyloid diseases is emphasised by other authors.[26] It is also thought that conversion of PrPC to PrPSc occurs due to a similar factor with chaperone.[27]

Some sources have shown a link between neuroinflammation and misfolding.[21] This case supports our modular chemical hypothesis. The formation of misfolding is proof that in prion diseases chemical or biochemical modules are formed based on molecular recognition.[28]

PrPC protein has functions many of which are still unknown. The attention of scientists has been focused on the fact that its misfolding is a crucial event in the prion disease. More specifically, the spread of prions occurs by conversion of PrPC to PrPSc, when the latter acts as a template. The proposed model above opposes this idea. Primarily, the formation of infectious PrPSc protein is genetic event and as such, it implies that one or more mutations occurred in the PRNP gene, which are expressed in the primary structure and the three-dimensional conformation of the protein. Conformational changes of the protein PrP formed by the PRNP gene are not recognized by its respective chaperone. In this state, the chaperones do not act on with the newly formed polypeptide chains. First, their lack of participation leads to the formation of a misfolded protein. The misfold is a characteristic of PrPSc protein, which causes some neurodegenerative diseases in mammals, including humans. Secondly, the lack of interaction of the newly synthetized protein with its respective chaperones, leads to the conformational instability, which results in the malfunction of the homeostatic machinery.

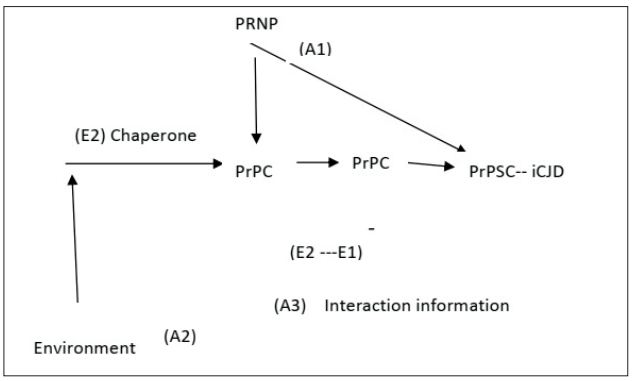

Figure 3. Multi modular model of sCJD

This model also explains the genetic etiology of the prion disease.

How can the prion disease be acquired after surgical interventions or after having had contaminated food?

We support the idea that chaperones are proteins and as such, they can be affected by mutations. If there is a mutation in the gene or in the genes responsible for the chaperones that take part in the conformation of PrPC protein, then prion diseases, just like the mutations in PRNP gene, will be considered as inherited and not acquired ones. There are other explanations. An alternative explanation is the phenomenon of somatic mutations.

We think that the acquired prion diseases manifest because of the inactivation of molecular chaperones. However, we have no evidence to prove our ideas. The value of these proposals lies in the idea that prion diseases are not caused by any infectious agent, and more so, when such agent is thought to bear the properties of a living organism.

Prion diseases are specific states of living organisms. In any of the cases, the study of prion diseases should be based on the recognition and identification of structures that carry biological information, from which certain processes and behaviours are formed.

5. CONCLUSIONS

Prion diseases results from chemical information between PRNP gene product and one or more protein chaperone genes. In these diseases, beside two genetic modules of PRNP gene and the gene or chaperone genes, chemical modules are formed.

The structure of chemical module is formed by PRNP gene product and from one or more protein chaperone genes.

In this study, we propose that gCJD individuals are mutants for both genes and sCJD individuals are mutants for the gene or genes of protein chaperone genes. Chemical module serves as a proof of iCJD formation. In these cases, a healthy individual is contaminated from mutant chaperones taken from gCJD and sCJD individuals. In this context, the fact that inflammation causes misfolding serves as a proof that interaction information and the respective chemical modules formation plays an important role in the appearance of prion

diseases.[21]

It is true that prions had challenged the fundamental concepts of heredity and infection, in reality another concept is distinguished and that is information, which cannot attributed only to nucleic acids.[26] The formation of chemical modules in the case of prion diseases proves the facts mentioned above.

LIST OF ABBREVIATIONS

PrPC – native conformation of cellular prion protein
PrPSc – prion protein scrapie (pathological isoform)
PRNP gene – coding gene of the prion protein
XChap – chaperone gene (chaperone protein hypothesis)
gCJD – genetic Creutzfeldt-Jakob disease
sCJD – sporadic Creutzfeldt-Jacob disease
iCJD – iatrogenic Creutzfeldt-Jacob disease

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