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REVIEWS
AND THEORETICAL ARTICLES

Prions as Non-Canonical Hereditary Factors

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Abstract—The present review concerns the diversity of prions (proteinaceous infectious particles) and the mechanisms of their reproduction. Various strains of the same prion are considered. We demonstrate that any prion strain regardless its molecular organization and species identity, under passaging on the isogenic homozygous background, is *per se* a virus-like hereditary factor. Its features depend on (i) the amino acid sequence of the prion protein that is encoded by the nucleotide sequence of the corresponding gene, and (ii) the state of the prion protein. Alteration of any of these two parameters, if stable and non-lethal, leads to a novel strain of the prion. Thus, contrast to canonical hereditary factors, prion strains are of more complex (bimodular) molecular nature. The bimodular principle is also very useful for describing any prion$^-$ states. Inclusion of prions in the general system of hereditary factors is considered.

Keywords: protein-based inheritance, prions, prion strains, bimodular hereditary factors
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INTRODUCTION

Prions (proteinaceous infectious particles [1–3]) are highly diverse in their molecular organization. Most of them are amyloids—fibril protein aggregates possessing clear cross-beta structures [4–6]. Such aggregates are able to grow by attaching new prion protein molecules which conformation is changed from native to amyloid, and then to undergo fragmentation due to the action of specific chaperones, thus leading to the appearance of new generations of the aggregates with the same properties [4–6]. Amyloid prions are known in the yeast *Saccharomyces* [6, 7], filamentous fungus *Podospora anserina* [8] and some mammals, including humans [3–5].

In addition to amyloid prions, some other ones exist as well. To date, they have only been identified in fungi. In these cases, the prionized state of the protein is reproduced by some autocatalytic processes. In particular, non-amyloid prions underlain by protein phosphorylation [9], chemical modification of histones [10], proteolytic cleavage [11], and interaction between nonhomologous proteins [12] have been described. The variety of these mechanisms suggests that any or almost any molecular process capable of maintaining the altered state of a protein through some positive feedback can potentially produce non-amyloid prions.

Mammalian prions deserve close attention since they induce severe neurodegenerative pathologies that are not yet curable [13, 14]. Fungal prions are of interest from two perspectives. First, fungal amyloid prions are a convenient model for detailing the mechanisms of amyloid aggregate formation [15]; this task is rather difficult to solve in mammals. Second, fungal prions are capable of being transmitted through cell divisions and thus are non-canonical hereditary factors [5, 6, 16]. A comprehensive study of such prions is essential for the construction of modern genetic theories encompassing the entire diversity of hereditary factors, both canonical and non-canonical.

Until now, all fundamental genetic theories (chromosome theory of heredity, the theory of mutation process, Central dogma of molecular biology, synthetic theory of evolution, etc.) are based on more than 50-year-old statement that DNA (in some viruses, genomic RNA) is the only material of heredity. Since hereditary prions do not fit this paradigm (they are of epigenetic, or more specifically, protein nature), the terminology used for their description is unrelated to the key genetic concepts. Moreover, prion terminology has been formed in isolation from that of other epigenetic hereditary factors, such as epialleles produced by DNA methylation or chemical modification of histones. As a result, genetic factual material has been fragmented into many disparate strands, hindering the development of modern general genetic concepts.

This problem can be successfully overcome. The fact is that the same hereditary prion can be represented by many different variants (strains), including those that differ significantly in their properties [17, 18]. A clear analogy with different alleles of the same gene is quite evident here. Regarding to this, we are entitled to consider different variants of the same prion as *prion alleles* [16]. The properties of each prion allele are jointly determined by two parameters: first, the

amino acid sequence of the prion protein, which is determined by the nucleotide sequence of the corresponding gene and, second, the specific state of this protein. Thereby, any prion allele is a *bimodular* hereditary factor whose properties are determined by the interaction of a *DNA determinant* and an *epigenetic determinant* [16]. For example, in the case of yeast prion [*PSI*$^+$] (amyloid aggregates of misfolded SUP35p molecules [6, 7]), the DNA determinant is a particular nucleotide sequence of the *SUP35* gene, while the epigenetic one is a particular variant of SUP35p amyloid conformation.

The proposed *bimodularity principle* is very convenient for describing any prion alleles as well as any prion lacking states. In particular, a certain [*PSI*$^+$] allele is designated as *SUP35*^{i}[*PSI*$^+$]^j, where *i* and *j* symbolize the corresponding DNA and epigenetic determinants. By analogy, a certain [*psi*$^-$] state (the absence of prion, i.e. the native conformation of prion protein) is designated as *SUP35*^{i}[*psi*$^-$]. Depending on the DNA determinant, such *prion null-alleles* significantly vary in their phenotypic manifestations, for example, in their ability to convert into [*PSI*$^+$] state (see below).

The bimodularity principle relates not only to prions. It is universal for any epigenetic hereditary factors regardless their particular molecular organization [19], thus opening up good prospects in the integration of various branches of epigenetics. In the present review, we demonstrate that mammalian prions are also embraced by the bimodularity principle.

MAMMALIAN PRIONS

The ability to produce prions has been clearly proven or is highly probable for at least five mammalian proteins: PrP, α-synuclein, tau-protein, Cu/Zn superoxide dismutase, and beta-amyloid peptide. Their properties have been reviewed in detail in numerous reviews [7, 8, 20]; thereby, we will concentrate only on the details directly relevant to the bimodular principle.

The most well-studied mammalian prion is PrP^{Sc}, an amyloid form of a protein encoded by the *PRNP* (prion protein) gene. This prion is accumulated in the cytoplasm of numerous cell types, mainly in follicular dendritic cells and neurons of the central nervous system. PrP^{Sc} is infectious by injection as well as through natural transmission between organisms via the digestive system or various fluids. It is capable of crossing some, but not all, interspecies barriers [21].

Amyloid aggregates of α-synuclein, a small protein encoded by the *SNCA* gene, are also localised in the cytoplasm. They are produced in brain neurons, mainly in *substantia nigra*, and can be transferred to healthy individuals [22]. However, such transmission is only possible by injection.

Tau protein is a range of related polypeptides produced due to alternative splicing of the primary transcript of the *MAPT* gene. When being hyperphosphorylated, this protein forms amyloid aggregates that accumulate in the cytoplasm of various brain neurons. The infectivity of these aggregates at the cellular level is not in doubt, but their ability to be transmitted between organisms is still debatable [23].

Molecules of Cu/Zn superoxide dismutase (product of the *SOD1* gene) become misfolded under certain circumstances, thus resulting in the formation of cytoplasmically localized amyloid aggregates in spinal cord neurons. Subsequently, these amyloids progressively spread to adjacent cells [24], but cases of their transmission from one organism to another are yet unknown.

Beta-amyloid peptide is produced due to proteolysis of a protein encoded by the *APP* (transmembrane amyloid precursor protein) gene. Contrast to abovementioned mammalian prions, amyloid aggregates of this protein (Aß) are localized in brain intercellular spaces. Numerous indirect data suggest that these aggregates can be transmitted between organisms [25], but no reliable confirmation has yet been obtained.

None of the listed mammalian prions are found in gametes or stem cells. Accordingly, it is accepted that these prions are non-heritable either meiotically or mitotically. Nevertheless, there are a number of arguments allowing mammalian prions to be considered as specific hereditary factors.

DIVERSITY OF THE WAYS OF INHERITANCE

Heritability refers to the ability of biological entities to transmit their characteristics (more precisely, the underlying factors) from ancestors to offspring. As usual, such a transmission occurs through cell division or fusion (fertilization, conjugation, cytoduction, etc.); this way is called *cell-to-cell inheritance* (Fig. 1a) [26, 27]. However, some other ways of hereditary factor transmission also exist.

One is *body-to-body inheritance* [26, 27]: an offspring receives some hereditary factors from its parent, but in a non-canonical way. In mammals, this phenomenon can be based on the transfer of some reproducible molecules from the mother's soma to the fetus via placenta. The reality of such a way of inheritance has been proven in muntjacs (*Muntiacus reevesi*) and wapiti (*Cervus canadensis nelsoni*); in the latter, PrP aggregates are efficiently transferred to the fetus from the mother not only under laboratory conditions but also in nature [28, 29]. This is, *per se*, a horizontal transfer of protein hereditary factors from parent to offspring (Fig. 1b). Infections arising from PrP aggregate transfer through the digestive system [21] are examples of similar horizontal transfer, but between unrelated individuals.

Another way of inheritance is characteristic of viruses. Despite their non-cellular organization, viruses are widely used as model genetic objects. In particular, bacteriophage T4 played an important role in demonstration of gene divisibility [30, 31]. Viral

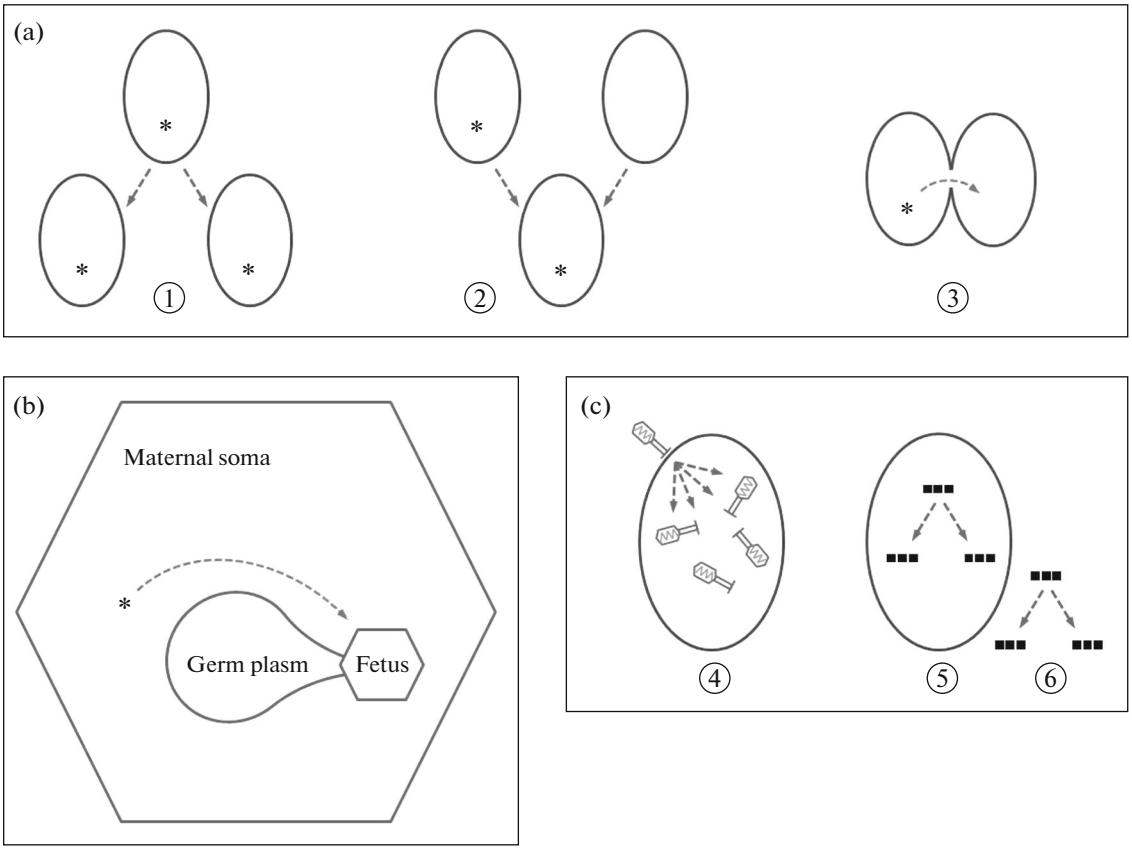

Fig. 1. Ways of inheritance. (a) Generalized scheme of cell-to-cell inheritance; (b) generalized scheme of body-to-body inheritance by the example of trans-placental transmission in mammals; (c) generalized scheme of virus-to-virus and prion-to-prion inheritance. Designations: ovals are cells; hexagons are multicellular organisms; asterisks are hereditary factors irrespective of their molecular nature and localization; filled squares are prionized proteins by the example of amyloids. Numbers in circles: 1—cell division; 2—cell fusion; 3—cell conjugation; 4—reproduction of viral particles; 5—reproduction of intracellular prion particles; 6—reproduction of intercellular prion particles.

heredity fits none of the two abovementioned ways. Indeed in this case the biological objects are not organisms or cells but viral particles. Organisms or individual cells are only used as the "external environment" necessary for viral particles to multiply and to reveal their hereditary properties.

Like viruses, prions do not possess cellular organization and also need organisms or individual cells as an "external environment" for reproduction. However, since the molecular organization of viruses and prions is not identical, it is reasonable to distinguish two close ways of inheritance: *from virus to virus* and *from prion to prion* (Fig. 1c).

To demonstrate general patterns of inheritance from prion to prion, we will consider different variants (strains) of the same prion in fungi and mammals.

VARIANTS OF THE SAME PRION IN FUNGI

To date, the highest number of fungal prion variants (at least several hundred) has been obtained in the yeast prion [*PSI*$^+$]. These variants can differ in their amino acid sequences, amyloid morphology, the portion of prionized SUP35p, interaction with specific mutations, mitotic and/or meiotic stability, phenotypic manifestation, and some other features [16–18]. Below, we will briefly consider a few examples of this diversity.

In its native conformation, SUP35p is a eukaryotic translation termination factor [32]. Being prionized, it loses this function, thus reducing the efficiency of translation termination at all three types of nonsense-codons. Therefore, [*PSI*$^+$] phenotypically manifests as an omnipotent nonsense suppressor [33]. Depending on a particular [*PSI*$^+$] variant, the efficiency of nonsense suppression varies considerably, resulting in a distinction between strong and weak variants ([*PSI*$^+$]^S and [*PSI*$^+$]^W, respectively). Some [*PSI*$^+$] variants are so weak that provide almost no suppression [34].

Due to its cytoplasmic localization, [*PSI*$^+$] behaves as a non-chromosomal hereditary factor. As a rule, strong variants show high stability both in mitosis and meiosis (all the progeny of the [*PSI*$^+$] cell receive this prion). The stability of some weak variants is significantly lower, sometimes up to 40–60% [17]. So-called "toxic variants" possess extra low stability [35]; however, this is due to selection against the cells with cor-

responding [*PSI*$^+$] variant, not to impaired reproduction of prion aggregates.

The abovementioned toxicity may result from an interaction between certain [*PSI*$^+$] variants and specific mutations. For example, when combined with the mutant *sup45-2* allele, which itself has the properties of an omnipotent suppressor, some [*PSI*$^+$] variants cause a dominant lethal effect [34]. Several other genes are also involved in this interaction [35, 36].

The ability of SUP35p to undergo prionization largely depends on its amino acid sequence, which is determined by the nucleotide sequence of the *SUP35* gene. The normal product of this gene contains three domains (N, M, and C). The latter is essential for cell viability [36, 37]; thereby, the studied changes of SUP35p amino acid sequence are localized mainly in N and M domains. Many dozens of such changes have been studied to date, and some of them significantly affect [*PSI*$^+$] properties [15, 38–42]. The N-domain is absolutely essential for prionization, and is therefore called the "prion domain". Under its absence (i.e., when the corresponding gene region is deleted), SUP35p is unable to produce [*PSI*$^+$] [37, 38].

As a rule, prionization embraces not all SUP35p molecules; some of them retain their native state, otherwise the cell will die due to the loss of the essential function of the C domain. The portion of prionized SUP35p significantly varies in different [*PSI*$^+$] variants: in [*PSI*$^+$]^S it is usually higher than in [*PSI*$^+$]^W [40, 43].

Any [*PSI*$^+$] particle is an amyloid fibril wherein all the molecules possess similarly arranged cross-ß structures serving as a conformational template for new generations of SUP35p aggregates. However, this protein can acquire numerous amyloid conformations differing in spatial organization and the number of the cross-ß structures (see [6, 15]). Even molecules with identical amino acid sequence can aggregate in different ways thus producing phenotypically distinct [*PSI*$^+$] variants [15, 44].

Under appropriate circumstances, each [*PSI*$^+$] variant is heritable: it produces new generations of prion particles with the same properties. The existence of at least several heritable variants has been demonstrated for a number of other fungal prions, including [*PIN*$^+$] and [*URE3*] in yeast *Saccharomyces*, and [*Het-S*] in *Podospora anserina* [17, 18, 40, 45, 46]. Similar situation can easily be obtained for any other yeast prion: it is enough to prionize the molecules of the corresponding protein that differ by at least one amino acid residue. Even if the resulting variants turn out to be phenotypically indistinguishable, they will be different, just like different alleles in case of silent nucleotide polymorphism.

STRAINS OF THE SAME PRION IN MAMMALS

In mammals, different variants of the same prion are commonly referred to as strains. Numerous PrP^{Sc} strains in sheep, goats, cattle, deer, mink, hamsters, mice, and humans are a spectacular illustration of this phenomenon [47–50]. Each PrP^{Sc} strain, if sufficiently stable, displays a number of properties that persist through multiple passages in organisms/cells of a particular species. Some examples of this diversity are briefly discussed below.

To produce PrP^{Sc} or to perpetuate it after infection, an organism/cell requires the *PRNP* gene [51]. Moreover, certain properties of PrP^{Sc} depend on the specific nucleotide sequences of this gene. First of all, this concerns the amino acid sequence of PrP; other prion characteristics can also be affected. For example, in murine PrP^{Sc} strains simultaneously carrying 108L and 189T, the incubation period is shorter than in strains carrying 108F and 189V [52]. If PrP^{Sc} is transferred to an organism/cell with a novel nucleotide sequence of *PRNP*, PrP molecules with at least one amino acid difference are formed, and a novel prion strain emerges. It does not matter whether it is phenotypically distinct from the "parental" one (see the section on variants of the same prion in fungi). Thus, each PrP^{Sc} strain can be reproduced only on a certain nucleotide sequence of the *PRNP* gene.

At the molecular level, different PrP^{Sc} strains can also be distinguished by some other characteristics including glycosylation patterns [53], resistance to chaotropic agents [54], resistance to proteinase K [55], and electrophoretic mobility following proteinase K digestion [56]. The latter is of special interest. If two or more PrP^{Sc} strains produced on the same homozygous *PRNP* background and thus identical in their amino acid sequences are nevertheless distinct in electrophoretic mobility, this fact is considered as a result of different amyloid conformations [49]. The Drowsy (DY) and Hyper (HY) PrP^{Sc} strains in golden hamsters are a well-known illustration of such diversity [57].

Different PrP^{Sc} strains can also be delineated by their clinical manifestations. One of these is prion deposition areas within the brain. For example, ovine PrP^{Sc} strains 22L and ME7, when transmitted to C57BL/10 mice, were shown to influence different brain regions: the former provided prion formation preferably in astroglia, while the latter mainly affected neurons and neuropil [58].

Another important clinical manifestation of a certain PrP^{Sc} strain is specificity of the induced behavioral lesion. The abovementioned DY and HY hamster strains are drastically distinct in this property; the behavioral effect of DY is lethargy, whereas HY results in hyperexcitability. The corresponding incubation periods are also different: in case of DY the onset of lesion occurs almost 3 times slower than of HY [57].

All the set of molecular (in vitro) and clinical (in vivo) characteristics of a certain PrP^{Sc} strain is pertained through serial passages on the isogenic DNA background. This means that new generations of the prion particles inherit all the features of their "ancestor.". Thereby, when reproduced on the isogenic DNA background, the particles of a certain PrP^{Sc} strain rep-

resent epigenetic hereditary factor in prion-to-prion way of inheritance (Fig. 1c).

The same principle is fully applicable to Aß [59]. Moreover, it covers any other mammalian prion, if some strains differing by just a single amino acid residue or by details of amyloid conformation are obtained.

MAMMALIAN PRIONS AS BIMODULAR HEREDITARY FACTORS

As abovementioned, under reproduction on the isogenic DNA background, any mammalian prion strain represents, like a fungal prion variant, an epigenetic hereditary factor, the subject of prion-to-prion inheritance. Therefore, we will further designate mammalian prions in italic, as it is used in case of yeast prions. We will also put this symbol in curly brackets ({PrP^{Sc}}, {*A*β}, etc.). This is due to the following reasons. First, prions possess non-nuclear localization, which is usually denoted in fungi by straight brackets ([PSI^{+}], [PIN^{+}], [*URE3*], [*Het-S*], etc.). Second, mammalian prions, unlike fungal ones, are not transmittable to daughter organisms/cells via cell divisions or fusions. Exactly to reflect this specificity, we will use for mammalian prions curly, not straight brackets.

That a certain mammalian prion exists as a multitude of different strains completely fits the fundamental genetic rule stating that a gene (in its classical sense, not limited to any molecular details) is represented by numerous alleles. Thus, different strains of the same mammalian prion could be considered as its allelic forms. Previously [16], the term "prion allele" was used only for fungal prions, but now we extend it to mammalian prions as well.

It should be clarified that this term is applicable only to the strains cultivated in the organisms/cells of the same species. For example, ovine {PrP^{Sc}} strains 22L and ME7 are allelic to each other, the same relates to their murine derivatives; however, 22L and the result of its adaptation in mice are not allelic, but orthologous. This is because the amino acid sequences of murine and ovine PrP are encoded by orthologous DNA sequences (orthologous DNA sequences are not allelic to each other).

Thus, the properties of a certain prion allele are cooperatively determined by (i) the nucleotide sequence of prion protein-encoding gene, and (ii) specificity of the state of prion protein. This means that any prion alleles can be regarded to as bimodular hereditary factors [16]. In particular, a certain {PrP^{Sc}} allele can be designated as $PRNP^{i}\{PrP^{Sc}\}^{j}$, wherein $PRNP^{i}$ is a DNA determinant (a particular *PRNP* sequence), and $\{PrP^{Sc}\}^{j}$ is an epigenetic determinant (a particular {PrP^{Sc}} conformation). If mammalian prions from different species are compared, species affiliation of *PRNP* is also required. For example, the aforementioned 22L and ME7 {PrP^{Sc}} ovine (*Ovis aries*) strains can be designated as $OaPRNP\{PrP^{Sc}\}^{22L}$ and $OaPRNP\{PrP^{Sc}\}^{ME7}$, with appropriate detalization of *OaPRNP* nucleotide sequences. If these prion alleles are adapted in mice, the resulting orthologs will be $MmPRNP\{PrP^{Sc}\}^{22L}$ and $MmPRNP\{PrP^{Sc}\}^{ME7}$, again with detalization of the DNA determinants.

Sometimes, during prion adaptation to a novel DNA determinant, the epigenetic determinant remains unchanged; this seems to be quite typical for yeast [16]. Meanwhile, in mammals, the epigenetic determinant usually becomes modified during adaptation (initial $\{PrP^{Sc}\}^{j}$ is altered into $\{PrP^{Sc}\}^{j*}$). This can result in so called "*prion mutations*," especially common when prion is transferred to another species [60]. In the simplest case, the transmitted prion allele might be replaced with a single novel one; however, the "ancestral" epigenetic determinant often produces a mixture of its novel derivatives (see [49]). Moreover, this mixture can be unstable thus requiring serial subsequent passages for selection of novel prion allele(s) [61, 62]. At the first glance, this complexity has nothing to do with general regularities of mutation process. Nevertheless, even canonical base pair substitutions in DNA are not single-step events: they occur through a prolonged primary lesion state, during which various mechanisms of DNA repair can significantly affect the eventual results (see [63]).

The bimodularity principle also allows explaining stable co-existence of different prion alleles in the same organism/cell. First, if an organism/cell is heterozygous for *PRNP*, two {PrP^{Sc}} alleles distinct in their DNA determinants ($PRNP^{x}\{PrP^{Sc}\}^{j}$, $PRNP^{y}\{PrP^{Sc}\}^{j}$) can be co-produced. Such a scenario is possible in case the protein molecules distinct in their amino acid sequences cannot be included in the same aggregate. Second, an organism/cell homozygous for *PRNP* might be an *epigenetic heterozygote* displaying co-existence of several {PrP^{Sc}} alleles distinct in their epigenetic determinants ($PRNP^{i}\{PrP^{Sc}\}^{x}$, $PRNP^{i}\{PrP^{Sc}\}^{y}$, $PRNP^{i}\{PrP^{Sc}\}^{z}$, etc.). Third, both aforementioned scenarios might be combined resulting in a complicated mixture of prion alleles.

As noted above, mammalian prion alleles are also known for {*A*ß} [59, 64]. By analogy with $PRNP^{i}\{PrP^{Sc}\}^{j}$, a certain {*A*ß} allele can be designated as $APP^{i}\{A\beta\}^{j}$. Herein, curly brackets additionally indicate that the prion particles may be produced and propagated even outside the cells, in the intercellular space. However, such a detail brings no changes into the essence of prion-to-prion inheritance (Fig. 1c).

PRION NULL-ALLELES IN MAMMALS

One of the possible states of a certain gene is its null-allele, the complete absence of the gene. By analogy, the absence of {PrP^{Sc}} could be regarded to as a prion null-allele. This state is conventionally designated as (native PrP conformation), but it would be more reasonable to use small letters, {prp^{C}} (like [psi^{-}] in yeast). It should be stressed out that similarity between [psi^{-}] and {prp^{C}} is not limited to the lack of

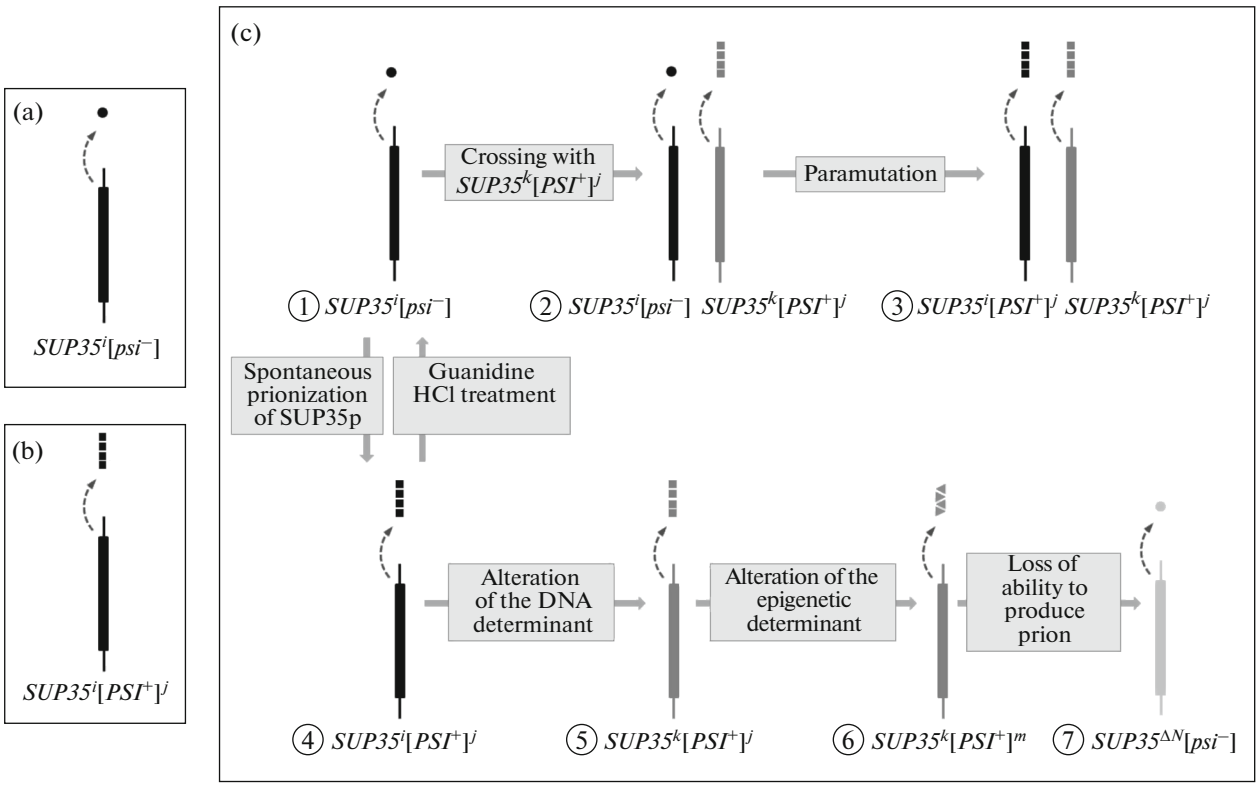

Fig. 2. Alterations of prion alleles and prion null-alleles, by the example of [*PSI*$^+$] and [*psi*$^-$]. (a) Generalized scheme of a [*psi*$^-$] allele; (b) generalized scheme of a [*PSI*$^+$] allele; (c) various alteration of [*PSI*$^+$] and [*psi*$^-$] alleles. Designations: filled rectangles are *SUP35* sequences; filled circles are native SUP35p; filled squares and triangles are different variants of SUP35p prionization; black, dark grey, and light grey colors correspond to distinct DNA determinants and the resulting differences in the amino acid sequences. Numbers in circles: 1—a [*psi*$^-$] allele convertible into [*PSI*$^+$]; 2—a [*psi*$^-$]/[*PSI*$^+$] heterozygote produced immediately after fusion of the *SUP35*^{i}[*psi*$^-$] and *SUP35*^{k}[*PSI*$^+$]^j cells; 3—a heterozygote with two different [*PSI*$^+$] alleles produced due to paramutation in 2; 4—a [*PSI*$^+$] allele produced due to spontaneous prionization of SUP35p in 1; 5 —a novel prion allele produced due to alteration of the DNA determinant in 4; 6—a novel prion allele due to alteration of the epigenetic determinant in 5; 7—a [*psi*$^-$] allele inconvertible to [*PSI*$^+$]. For each prion allele or prion-null allele, its bimodular designation is presented. Alteration of any determinant or both, if non-lethal and stable, produces novel bimodular allele.

corresponding prion; various types of both [*psi*$^-$] and {*prp*^{C}} exist. We will briefly consider this fact below.

In yeast, three types of [*psi*$^-$] are distinguished. This division is based on their convertibility to [*PSI*$^+$] under prion transmission through either cytoduction or protein transformation. The first type is *SUP35*^{ref}[*psi*$^-$], wherein *ref* designates typical amino acid sequence of SUP35p with conventional polymorphism not affecting the properties of SUP35p. Such prion null-alleles can be prionized by a wide spectrum of the [*PSI*$^+$] templates [16, 65]. The second includes native SUP35p with non-conventional amino acid sequences requiring specific templates for conversion. *SUP35*^{PNM2}[*psi*$^-$] is one of the well-known cases [40]. The third is represented by *SUP35*$^{\Delta N}$[*psi*$^-$], native SUP35p lacking the prion domain; it completely fails prionization irrespective of which [*PSI*$^+$] templates are used [37, 38].

Although polymorphism of *PRNP* is studied much less than of *SUP35*, different {*prp*^{C}} alleles are already known, which vary in their convertibility to {*PrP*^{Sc}}. Let us illustrate this with several examples. Prion-null alleles *OaPRNP*^{VRQ}{*prp*^{C}} and *OaPNRP*^{ARR}{*prp*^{C}} contrastingly differ from each other in their susceptibility to common ovine {*PrP*^{Sc}}; the former is highly susceptible while the latter displays complete resistance [66]. Goat prion-null alleles *ChPNRP*^{K222}{*prp*^{C}} and *ChPRNP*^{Q222}{*prp*^{C}} are drastically distinct in the spectrum of amyloid {*PrP*^{Sc}} templates capable of providing their prionization [67]. Notably, complete deletion of *PRNP* (this gene is inessential for viability; [68]) results in such a prion null-allele that principally cannot be converted to {*PrP*^{Sc}}.

Notably, none mammalian prion null-allele analogous to *SUP35*$^{\Delta N}$[*psi*$^-$] in yeast have been identified so far. However, the general regularity becomes evident: the properties of a certain prion-null allele, whether it is fungal or mammalian, are determined not only by the lack of prion particles but also by the sequence of prion protein-encoding gene. Thus, the bimodularity principle is equally applicable to both prion alleles and prion-null alleles.

Table 1. Diversity of alleles in terms of their localization and molecular nature

Basics of division		Molecular nature of alleles	
		canonical	non-canonical
Localization of alleles	canonical (chromosomal)	Alleles produced by polymorphism in chromosomal DNA sequences[1]	Alleles produced by polymorphism in chromosomal DNA methylation and histone code[2]
	non-canonical (non-chromosomal)	Alleles produces by polymorphism in mitochondrial, plastid, nucleoid, plasmid, viral, etc. DNA sequences[3, 4]	Alleles produced by polymorphism in non-chromosomal heritable epigenetic marks such as prionized states of a protein, small RNAs, differences in cortex structure, alternative states of bacterial epigenes, etc. [19][3]

[1] Can provide Mendelian segregation.
[2] Can provide Mendelian segregation, if meiotically stable.
[3] Cannot provide Mendelian segregation.
[4] In some viruses, alleles are produced by polymorphism in RNA sequences.

CONCLUSIONS

The idea that proteins can perform hereditary functions is rather old. In the late 1920s, when the chromosome theory of inheritance was still taking shape, most geneticists believed that the genetic material was represented by proteins, not DNA [69, 70]. This viewpoint seemed to be quite reasonable due to higher structural complexity of proteins. Demonstration of the hereditary role of DNA [71, 72] buried this idea for several decades. As a result, the DNA theory of inheritance has been established [73], which postulated that any hereditary factors were represented by DNA sequences solely. All fundamental genetic terms (gene, allele, genotype, mutation, etc.) became tightly linked to DNA. The same happened with the term "genetic."

Several attempts to suggest at least partial hereditary role of the gene products [74–77] did not attract significant attention. Only after inheritance of cortex [78], centrioles [79], fungal prions [44, 80], histone code [81], and alternative states of bacterial epigenes [82] had been uncovered, the idea of protein-based inheritance became a part of genetics [83].

In prion studies, this idea has been transformed into the "protein-only hypothesis" [43, 56, 84, 85], according to which "*prion strain specificity is believed to be encoded at the level of protein conformation*" ([48, p. 99]). This hypothesis is true in that the infectious agent contains only protein. However, the wording "protein-only" may cause an erroneous impression that the features of the new generations of prion particles are predetermined only by the "ancestral" ones. But in reality, these features are co-determined by two factors: (i) a particular DNA sequence encoding the prion protein, and (ii) the state of this protein in the "ancestral" prion particles [50, 86, 87]. Thereby, the bimodularity principle is more adequate than the protein-only hypothesis. Moreover, this principle allows simple and useful designating various alterations of prion alleles and prion null-alleles (Fig. 2).

The first step towards the inclusion of prions in a general system of hereditary factors was made by Yu.O. Chernoff [83], who regarded the native and prionized states of SUP35p to as alleles. Further, Wickner et al. [88, 89] suggested considering fungal prions as protein genes. Tuite [90] pointed out that SUP35p conversion from its native to prionized state in a [psi$^-$] × [*PSI*$^+$] hybrid as a paramutation (alteration of one allele due to interaction with another one in a heterozygote) [91, 92]. In 2017, based on the mentioned ideas, we elaborated the concept of allelic forms of fungal prions, and proposed the bimodular principle for describing prion alleles and prion-null alleles [16]. Herein, we made the next step: we expanded our concept to mammalian prions.

The phenomenology of prion alleles in fungi and mammals is very similar. In both cases we are talking about protein infectious particles capable of cell-dependent reproduction with retention of their in vivo and in vitro characteristics (under propagation on the isogenic DNA background). At first glance, prion alleles seem to be some kind of exotic not worthy of inclusion in general genetic concepts. However, modern genetics is familiar with many non-canonical phenomena. In the early stages of the development of genetics, all hereditary factors had a chromosomal localization, which led to the chromosomal theory of heredity. But with the discovery of non-chromosomal inheritance, it became clear that there were alleles with non-canonical localization [93, 94]. Another canonical point of view was that all inherited factors were represented by DNA [73]. But this idea turned out to be incorrect as well: epigenetic heredity was discovered at the turn of the 20th and 21st centuries [95, 96]. Prion alleles are non-canonical both in their molecular nature and in their localization, thus giving logical completeness to the modern ideas about the diversity of hereditary factors (Table 1).

Table 2 illustrates basic analogies between prion-related and canonical genetic phenomena. Significant similarity between them opens good prospects for constructing modern genetic concepts that should equally cover all factual material in genetics, either canonical or not.

Table 2. Analogies between prion-related and canonical genetic phenomena

Prion-related phenomenon	Fungal example	Mammalian example	Its analog in canonical genetics
Prion	$[PSI^+]$	$\{PrP^{Sc}\}$	Gene
Prion allele	$SUP35^i[PSI^+]^j$	$PRNP^i\{PrP^{Sc}\}^j$	Allele
Prion null-allele	$SUP35^i[psi^-]$	$PRNP^i\{prp^C\}$	Null-allele
Co-existing variants of a prion protein, one of which is prionized and another is not	$SUP3^i[PSI^+]^j$ $SUP35^{\Delta N}[psi^-]$	Unknown so far	Heterozygote
Co-existing prion alleles distinct in their DNA determinant	$SUP3^i[PSI^+]^j$ $SUP35^k[PSI^+]^j$	$PRNP^i\{PrP^{Sc}\}^j$ $PRNP^k\{PrP^{Sc}\}^j$	
Co-existing prion alleles distinct in their epigenetic determinant	$SUP35^i[PSI^+]^m$ $SUP35^i[PSI^+]^n$	$PRNP^i\{PrP^{Sc}\}^m$ $PRNP^i\{PrP^{Sc}\}^n$	
Phenotypic manifestation of a $[PRION^+]$ allele in a stable $[PRION^+]/[prion^-]$ heterozygote	$SUP35^i[PSI^+]^j$ $SUP35^{\Delta N}[psi^-]$	Unknown so far	Dominant and recessive alleles
Prionization of native prion protein in the $[prion^-] \times [PRION^+]$ hybrid[1]	$SUP35^i[psi^-]$ $SUP35^i[PSI^+]^j \rightarrow$ $SUP35^i[PSI^+]^j$ $SUP35^i[PSI^+]^j$	Unknown so far	Homozygotization
	$SUP35^i[psi^-]$ $SUP35^k[PSI^+]^j \rightarrow$ $SUP35^i[PSI^+]^j$ $SUP35^k[PSI^+]^j$	Unknown so far	Paramutation
Prion transfer to a novel DNA background	$SUP35^i[PSI^+]^j \rightarrow SUP35^k[PSI^+]^j$	$PRNP^i\{PrP^{Sc}\}^i \rightarrow PRNP^k\{PrP^{Sc}\}^{i*}$	Transgenesis
Results of interspecies prion transfer	$ScSUP35[PSI^+]$, $SeSUP35[PSI^+]$	$OaPRNP\{PrP^{Sc}\}$, $MmPRNP\{PrP^{Sc}\}$	Orthologs
Propagation of a certain prion allele	production of new generations of the $SUP35^i[PSI^+]^j$ particles	Production of new generations of the $PRNP^i\{PrP^{Sc}\}^j$ particles	Replication of the genetic material
Interaction between different prions	interaction between $[SWI^+]$ and $[PIN^+]$[2]	Unknown so far	Intergenic complementation

[1] In case the protein molecules distinct in their amino acid sequences cannot be included in the same aggregate.
[2] [97].

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COMPLIANCE WITH ETHICAL STANDARDS

The present article does not contain any studies involving animals as subjects.

The present article does not contain any studies involving humans as subjects.

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