A new disease organism from plants – is it a prion?

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Abstract

A disease organism, "new to science", much publicised [1] but not published, has been found in GM "Roundup-Ready" Soya bean crops. It is claimed to cause foetal abnormalities and infertility in cattle and humans. "Roundup" is a herbicide which is a metal chelator. The hypothesis is that the new organism is actually a prion protein and that it is initiated in a similar manner to that postulated for Mad Cow Disease (bovine spongiform encephalopathy, BSE), induced by the insecticide Phosmet, which is also a metal chelator. Since that old and disputed postulate, several new findings now add greater evidence for it. That a similar process could occur in plants, appears possible since plants include similar characteristic amino acid domains and prions are of old evolutionary origins, also present in fungi. The hypothesis indicates some obvious further investigations, especially to determine amino acid rather than nucleotide sequences of the new organism. If these show any similarities to prion proteins then this would give some rationale to the claim of a new organism, and it would support the older hypothesis about the origins of BSE. It would widen the biological scope of the prion phenomenon and support the warning of a new emerging source of serious disease from this GM crop.

Introduction

Huber has described and much publicized [1], but not published, a possible disease organism that arises from "Roundup Ready" (RR) Soya crops (which are soya that is genetically engineered to resist Roundup, a weed killer whose active ingredient is glyphosate). The organism is "new to science," virus-sized but not a virus, is claimed to grow *in vitro* in the presence of cells, and may be the cause of infertility and miscarriage in cattle and humans. This would be a very serious finding if shown to be true; but it is easy to dismiss such claims. Huber has said that he will publish "when they have its sequence".

Huber's improbable finding would become more plausible if supported by a reasonable hypothesis that explains it. I suggest such a hypothesis here.

After "Mad cow disease" (bovine spongiform encephalopathy BSE) and the increase in other transmissable encephalopathies (TSEs) like CJD in the UK, it was a natural idea, shared with 2 or 3 colleagues, to suggest that the new organism may be a prion-like protein and therefore its sequence would be of amino acids and not of nucleotides.

It occurred to me that the new organism and BSE may both have been initiated in similar ways by the coincidence that metal chelating agents could be involved in both: glyphosate, (the active ingredient of Roundup herbicide widely used in herbicide resistant GM crops) in the case of the new organism and phosmet, the insecticide that was used to treat warble fly in cattle, in the case of BSE. This coincidence may be significant, and suggest that prions are the agents in both cases.

If this turns out to be the case then some contentious ideas about the origins of TSE prions would need to be re-considered.

The reported disease organism

Huber's powerpoint presentation[1] includes EM photos of the organism or "entity". These show nearly circular structures of about 25 to 50 nm, with an even spread of intermediate diameters but none larger or smaller. Lightening up dense areas in the EM photo reveals the fibrous nature of the particles, more like aggregates than a virus. One wonders whether there could be any relationship to the virus-like particles described in TSE-infected cells.[2]

The action of metal ions on the prion protein

There are many reviews of prion diseases, e.g.,[3] and prions in a wider context[4]. It is now generally accepted that the diseased (e.g., scrapie) PrP^{Sc} prion protein can cause the normal (cellular) PrP^{C} protein to refold into the PrP^{Sc} form; thereby the disease becomes self-replicating and transmissable. The question remains, how did the initial diseased PrP^{Sc} first arise from the normal cellular PrP^{C}? The terms "spontaneous" and "sporadic" applied to TSE diseases still hide our ignorance about their ultimate origins.

Recent findings about scrapie, BSE and fungal prions indicate how metal ions are involved in the initial 'abnormal' folding, and that similar processes are possible in plants. These findings lend support to the hypothesis as follows:

The mammalian PrP^{C} is a Cu protein [5, 6] with super-oxide dismutase activity [7]. There is evidence that the metal environment impacts on the onset of TSE, especially Mn, [8] Replacement of the Cu by Mn or other metal ions is one factor that induces some characteristic changes in folding to PrP^{Sc}, [9] causing aggregation and formation of (myeloid) fibres, [10, 11]. The transformation has been achieved in cell culture, in one case dependant on Mn ion or other metal ions and on the redox state of the medium, [12] and in another by adhesion to stainless steel [13] which apparently catalysed formation of PrP^{Sc}. The steel pins used were shown in previous studies of transmission of infection by surgical instruments, to be several times per unit area more effective than steel discs in binding PrP^{Sc}, [14] It may be significant that the pins were of 2% Mn steel, the discs without Mn. (see Supplementary to that paper and the steel suppliers' literature.) The PrP^{Sc} produced was different from the usual scrapie agent in its morphological disease effects, confirming *de novo* creation, and being another example of how a prion can fold into different forms.

Although there must be many factors involved, including intracellular [15] and environmental, [16] the above cell culture findings show that *de novo* creation of PrP^{Sc} from PrP^{C} is possible, and is probably related to metal or metal ion catalysis and therefore affected by chelating substances. The metal binding properties of glyphosate have been reviewed, [17]. Studies of phosmet deal mainly with its toxicity due to inhibition of acetylcholine esterase, a property probably shared by glyphosate.

The apparent involvement of metals in the origin of disease prions allows one to re-appraise Purdey's hypotheses, [18] Although the steel pin experiment is long and painstaking, it would be instructive to see if addition of Mn++ or of phosmet to the cell culture medium increases the proportions transformed. Phosmet does appear to increase amounts of the cellular prion on the cell membrane, [19]. There is no mention in the latter paper whether the chelating properties or Cu++ might be involved.

Are there prions in plants?

If plants contain prion-like sequences, then similar inducible changes would be expected. However, no prion-type proteins have been reported in plants. Prions in yeast and other fungi have been studied extensively and explain features of cytoplasmic non-genetic inheritance,[20] and provide models for multi-cellular organisms, [21]. The prion protein can have other functions than causing disease. The evolution of prion sequences has been traced to early eukaryotes and is related to the ZIP metal transporters, [22]. These are common in plants [23] but lack the characteristic sequences (high density of Asn and Gln residues) associated with prion replication. Asp/Gln domains are however common in plants [24]. Not all prion replication depends on such domains; the *Podospora* HET-S prion lacks them, yet is a self-replicating prion. Plant prions could exist therefore, either with or without Asp/Gln domains. Another common feature of prions, the characteristic peptide octa-repeats that bind Cu and are active anti-oxidants, have been found in plants [25]. These are inducible by ozone or other stress. All these features together suggest that

prion-like proteins are likely to exist in plants.

Conclusions

One can then conclude that Huber's new 'organism' could be a prion type protein generated by the particular conditions in "RR soya" crops. If this indeed turns out to be the case, then it makes this 'organism' not quite so "new to science" and gives it a rationale basis. This immediately suggests further experiments that may confirm or refute the idea. The first, obviously, is to check whether the organism is protein or nucleic acid or both. If protein, then its amino acid sequence compared to known prion sequences would provide useful evidence; if the sequence differs from fungal or vertebrate prions, then it might point to other proteins in plants that can self-replicate their structure. Such a finding would extend the biological phenomenon of non nucleic acid protein inheritance. The next question is, why have there been no other reports like Huber's? That it has not been found during the widespread use of Roundup as a weed-killer is not surprising, since the treated plants are killed. RR Soya however survives, setting a new situation. The finding needs to be repeated elsewhere and under controlled conditions, such as in pot culture or in plant cell culture. The phenomenon could be confined to soya grown in that region of the USA, depending on soil properties, temperature, or other environmental factors like ozone stress or on soya being a leguminous plant. RR canola (oil-seed rape) for example is grown in cooler climates and is not leguminous.

Comments

Whether the new 'organism' is actually a cause of disease remains the most important question, but the present hypothesis is concerned only to explain its origins, whether it is a prion-like molecule. It remains possible that, as in fungi, a plant prion could have other functions.

I publish this hypothesis now, in spite of the many doubts, to open the debate and to stimulate further work, because of the obvious importance of Huber's findings if shown to be valid. I hope that this paper might help towards a resolution of a potentially important finding.

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