Transmission of Prions and Alzheimer’s disease Abeta Amyloid

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Protein Misfolding Disorders

Alzheimer’s disease

Parkinson’s disease

Protein Misfolding and aggregation

Huntington’s disease

Diabetes type 2

Prion diseases

History of the Prion Hypothesis

Accidental transmission of scrapie in sheep
1937

Experimental transmission of scrapie in sheep
1939

Demonstration of small size of infectious agent
Kuru transmitted to Chimpanzee
1966

Infectious agent not affected by DNA elimination
• Protein-only hypothesis proposed by Griffith
1967

Prion protein isolated from the infectious agent
Prusiner coined the term prion
1982

Identification of the PrP gene
1985

PrP transgenic mice develop neurodegeneration
PrP knock out mice resistant to infection
1990
1993

Cell-free prion replication
Discovery of yeast prions
Efficient prion replication in vitro by PMCA
2001

In vitro generation of yeast prions
2000

In vitro generation of “bona-fide” infectivity in vitro by propagation of PrPSc
2004

Generation of “synthetic prions”
2005

In vitro generation of infectivity with defined components
De novo production of infectious prions
2007

Prions strains and species barrier reproduced in vitro
2008

First mutation in PrP linked to familial disease
1989

In vitro generation of yeast prions
1994

In vitro generation of infectivity with defined components
De novo production of infectious prions
2007

In vitro generation of “bona-fide” infectivity in vitro by propagation of PrPSc
2004

Expansion of the Prion Principle to Other Protein Misfolding Diseases

Soto (2011) TIBS 36: 151-158
Molecular basis of prion and amyloid formation

Prion replication process

Host PrPC + Infectious PrP<sup>Sc</sup>

Amyloid formation process

Addition of seed

The seeding mechanism has the intrinsic ability to be transmissible

Prions are protease-resistant amyloid-like β-sheet rich aggregates of diverse size, ranging from small oligomers to large aggregates all of which are seeding-competent.

Highly purified prions can induce disease when administered to individuals that without exposure would not develop the pathology.

Prions can be acquired by different routes of exposure, including: intra-cerebral injection, i.v. (blood transfusion), p.o. (oral ingestion), i.p., s.c., intra-ocular, intra-nasal, but not through skin contact or inhalation.

Prion transmission exhibit the phenomenon of strain variation and species barrier.

Prions are highly resistant to common sterilization procedures. They can resist extremely high temperatures, UV irradiation, treatment with detergents and enzymes (nucleases, proteases, etc).

Prions can tightly bind to various surfaces (such as soil, minerals, surgical tools) and maintain infectious properties for long periods of time.

Prions can penetrate biological membranes (intestinal, blood-brain barrier, plasma membrane) and be highly resistant to biological clearance.
Does Amyloid-beta spread like a prion?

De novo induction of amyloid-β deposition in vivo

R Morales¹,², C Duran-Aniotz¹,³, J Castilla²,⁴, LD Estrada²,⁵ and C Soto¹,²

Days after inoculation

Normal Brain | Alzheimer's Brain

285 d | 450 d | 585 d

Anti-Aβ antibody | Thioflavin S

40x | 200x

Antibody | Anti-GFAP antibody

HuAPPwt
585 dpi

Tg2576
365 days old
Amyloid Induction by Blood Transfusion

Tg2576 and WT

Animals challenged by tail vein route

WT transfused with Tg blood

Tg not treated

Tg transfused twice with WT blood

Tg with 1 transfusion

Tg with 2 transfusions

Sacrifice at 250 days old. Little spontaneous plaque development expected

Animals challenged by tail vein route

1st Transf. 50 days

2nd Transf. 80 days

Plaques Number/mm²

Aβ Burden (%)

Insoluble Aβ42 (ng/ml)

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Tg untreated

Tg with WTBlood

Tg with Tg blood

Tg + WTBlood (1 transfusion)

Tg + Tg blood (1 transfusion)

Tg + WTBlood (2 transfusions)

Tg + Tg blood (2 transfusions)

Tg + Tg blood + 10% BH (1 injection)

Tg untreated

Tg + WTBlood

Tg + Tg blood

Tg + Tg blood + 10% BH (1 injection)

Tg untreated

Tg + WTBlood

Tg + Tg blood

Tg + Tg blood + 10% BH (1 injection)
If misfolded seeds are circulating in blood and contribute to induce AD pathology in the brain... Then, can we decrease cerebral amyloid formation by removing Aβ seeds from the blood? Can these seeds be used as novel biomarkers for early diagnosis?

**Treatment**

**Diagnosis**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Diagnosis</th>
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<tbody>
<tr>
<td>SHAM</td>
<td><img src="image1" alt="Brain images" /></td>
</tr>
<tr>
<td>ThS</td>
<td><img src="image2" alt="Brain images" /></td>
</tr>
<tr>
<td>Blood exchanged</td>
<td><img src="image3" alt="Brain images" /></td>
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**Implications of seeding for Therapy and Diagnosis**
Many Open Questions

✓ Can we extrapolate results in animal models to the situation in humans?

✓ Is seeding/spreading = Infectivity?

✓ How are the first seeds formed?

✓ How seeds spreads among cells and tissues?

✓ What is the structure and composition of seeds?

✓ Do different type of Aβ aggregates behave like prion strains?

✓ Are there Aβ seeds in animals of consumption? If so, is there species barrier?

✓ Which possible practical routes of exposure (blood transfusion, contaminated surgical Instruments, ingestion of seed-containing food) represent a risk for human health?

✓ Is it possible to induce protein aggregation by cross-seeding with other disease-associated proteins or “functional” prions?