SEMINARIOS
Centro Nacional de Epidemiología

MINISTERIO DE ECONOMÍA Y COMPETITIVIDAD
Instituto de Salud Carlos III

Bases Moleculares de las Enfermedades Neurodegenerativas

Madrid, 13 de junio de 2019

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Molecular Basis of Neurodegenerative Disorders

Neurodegenerative Disorders are Conformational or Protein Misfolding Pathologies

1. Protein Misfolding and Conformational Conversion	→ Molecular Level
2. Transcellular Disease Propagation through brain networks	→ Cellular Level
3. Networks disintegration	→ Organ/Individual Level

- Enfermedades conformacionales
  - Conceptos de plegamiento de proteínas
- Encefalopatías Espongiformes Transmisibles como paradigma
  - Definición
  - Agente Patógeno - Prion (PrP^{C} vs PrP^{Sc})
  - Carácter infeccioso y transmisión
  - Diagnóstico molecular
- Más allá del principio del prion
  - Otras enfermedades neurodegenerativas
  - Otras enfermedades conformacionales (DMT2, patología vascular)
- Bases moleculares y celulares de la neurodegeneración
  - Nexopatías moleculares
  - Conceptos unificadores de las enfermedades neurodegenerativas
  - Correlación molecular-celular-epidemiológica

Classification of Diseases

- Inflammatory
- Degenerative
- Infectious
- Neoplastic
- Conformational or Protein Folding Disorders

Disorders of Protein Folding

- Systemic and cerebral amyloidosis
  - Alzheimer's disease (Amyloid β)
  - Prion diseases (PrP)
  - Parkinson's disease (α-synuclein)
- Tauopathies (tau, PHF)
- Polyglutamine repeats disorders
  - Huntington´s disease (huntingtin)
  - Spinobulbar muscular atrophy
- Amyotropic Lateral Sclerosis (SOD1, α-synuclein)
- Sickle cell anemia (Hb)
- Cataracts (cristallin)
- Cystic fibrosis (CFTCR)
- Type II diabetes (Insulin, IAPP (amylin))
- Atherosclerotic Lesion (TTR, ApoAI, γ-Ig, Medin, Aβ)

The accumulation of aggregates is damaging to cells & tissues

- aggregates absorb critical macromolecules, causing cell death
- dead cells release aggregates into extracellular matrix, causing tissue damage
- the most vulnerable organ is the brain

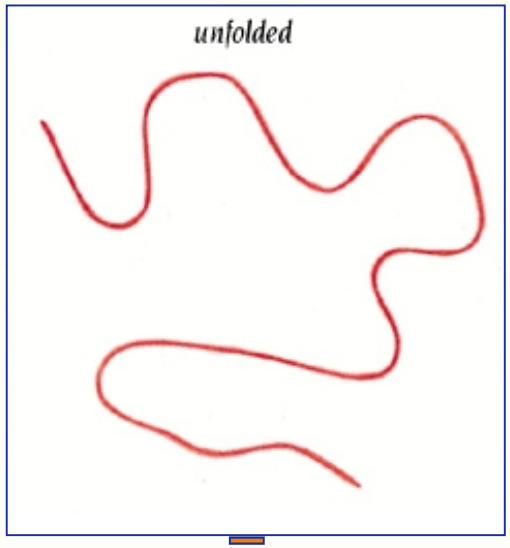
Anfinsen's classic experiment

Ribonuclease A

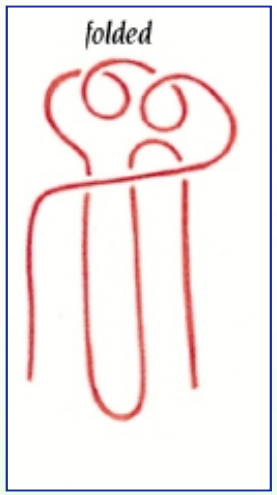
The aminoacid sequence determines univocally the three-dimensional structure of the proteins

The Central Dogma of Biology (J. Monod)

The Levinthal´s paradox



seconds/minutes



100 amino acids protein, 2 conf. states for each amino acid

$2^{100} = 1.3 \times 10^{30}$ different conformations

10^{-13} sec for each conformation

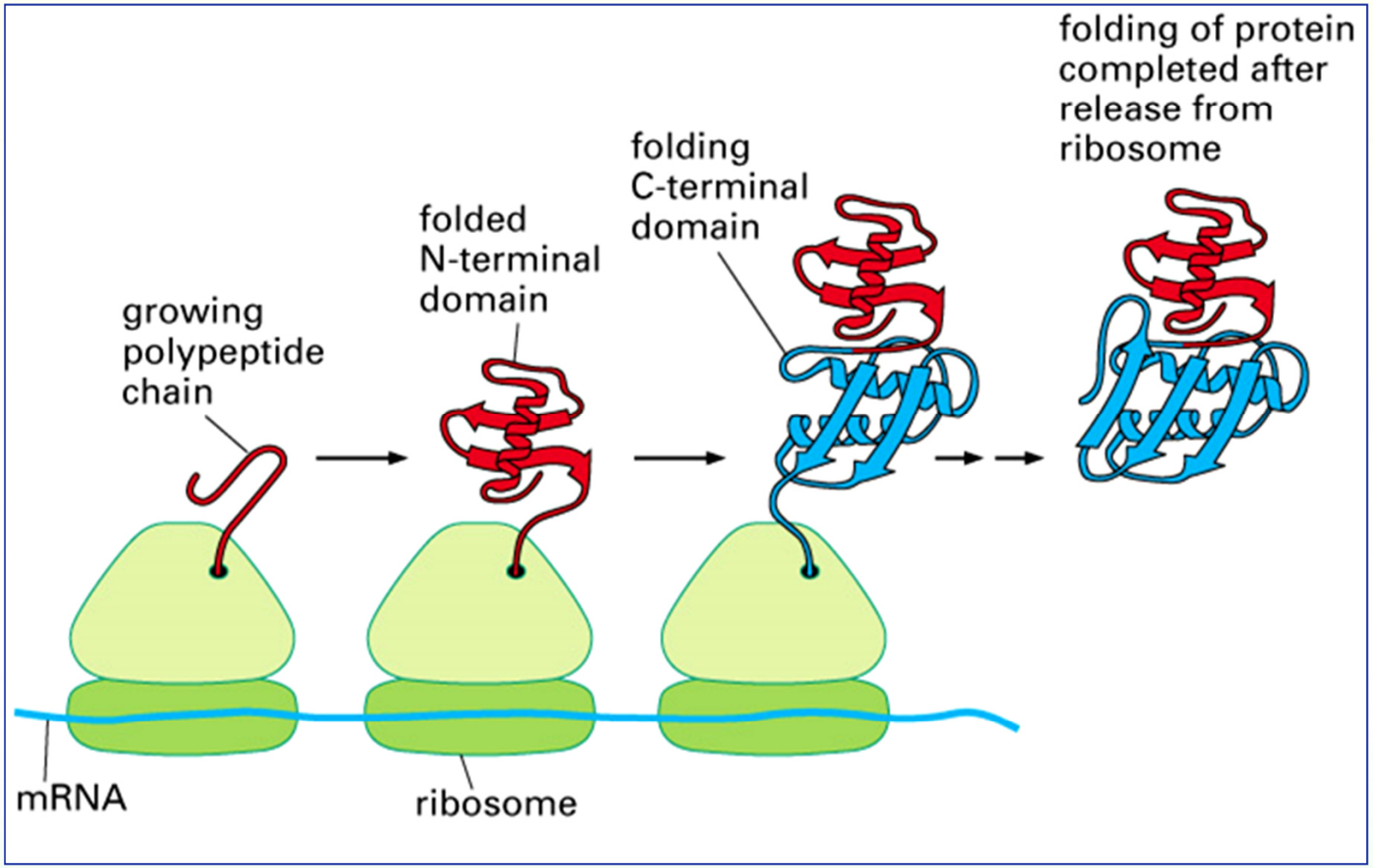
1.27×10^{17} seconds = 4×10^{9} years

Thus, exploring all folding conformations is impossible

Protein must have preferential pathway

- Major obstacle is trapping in a non-productive conformation
- Kinetic barriers:
  - –Aggregation of intermediates
  - –Proline isomerization
  - –Formation of incorrect disulfides

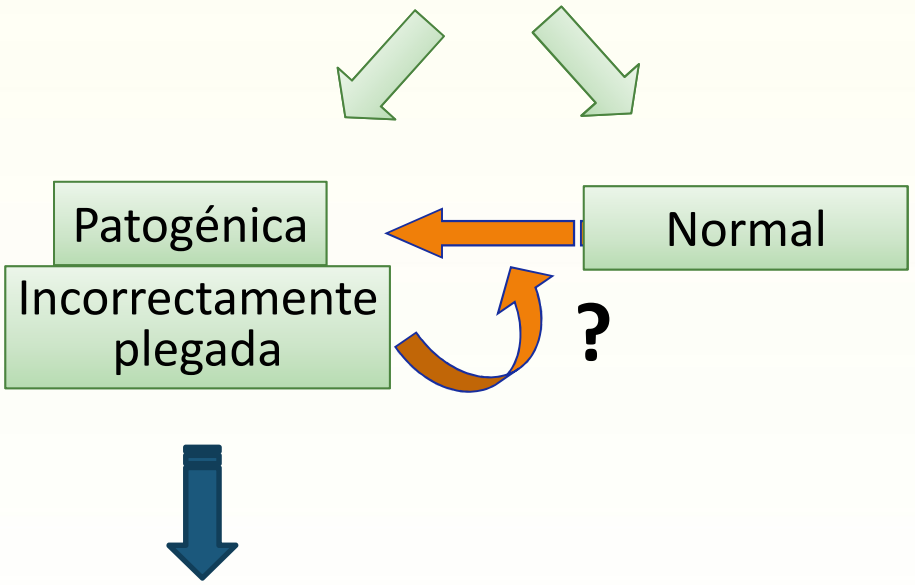
Folded Proteins emerge from the ribosome



1 SECUENCIA

2 CONFORMACIONES

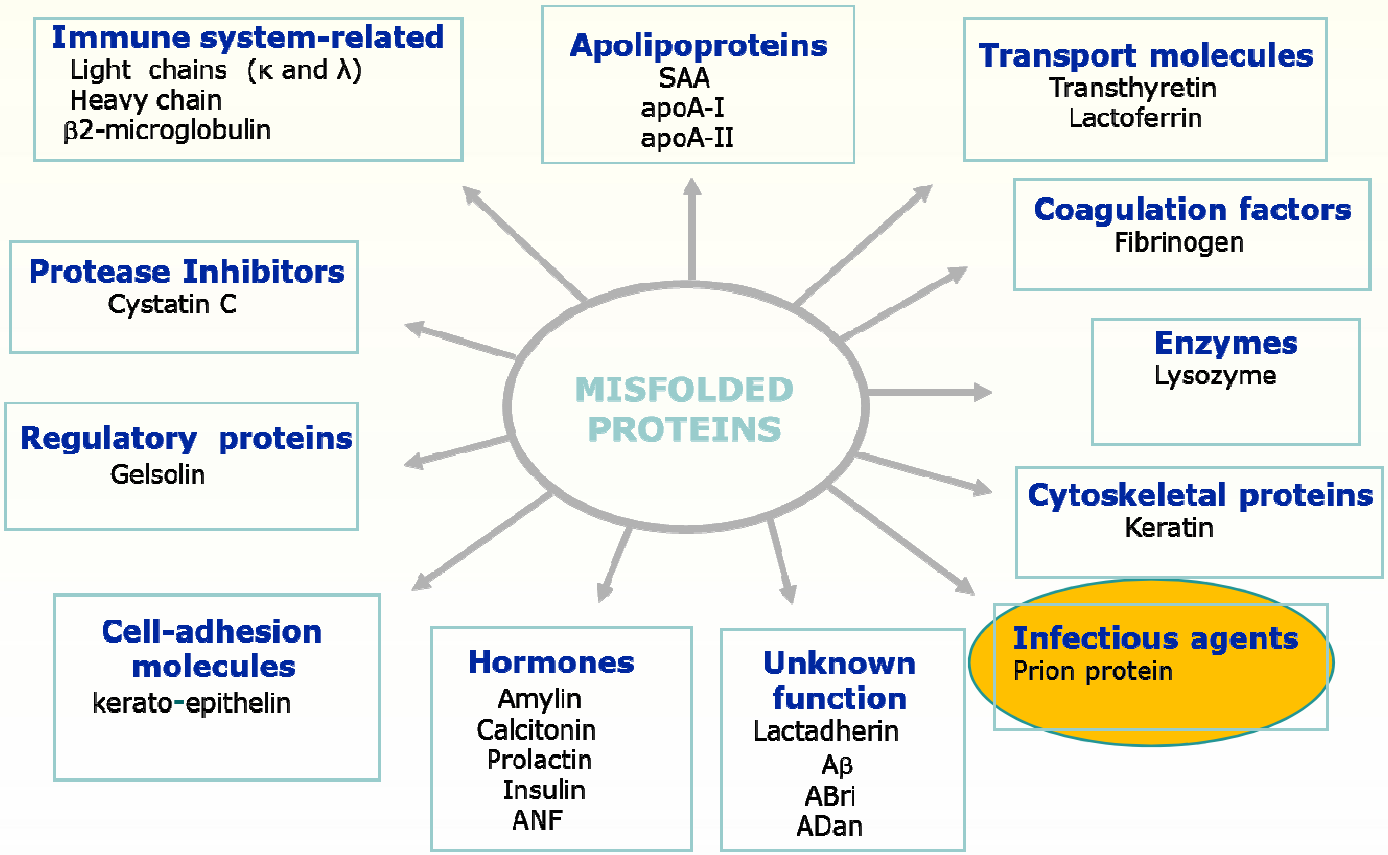
- Estructuras en hojas β↑
- Solubilidad↓
- Tendencia a agregar↑
- Resistancia a proteasas ↑



Daño celular y tisular mediado por la acumulación de depósitos insolubes (agregados)

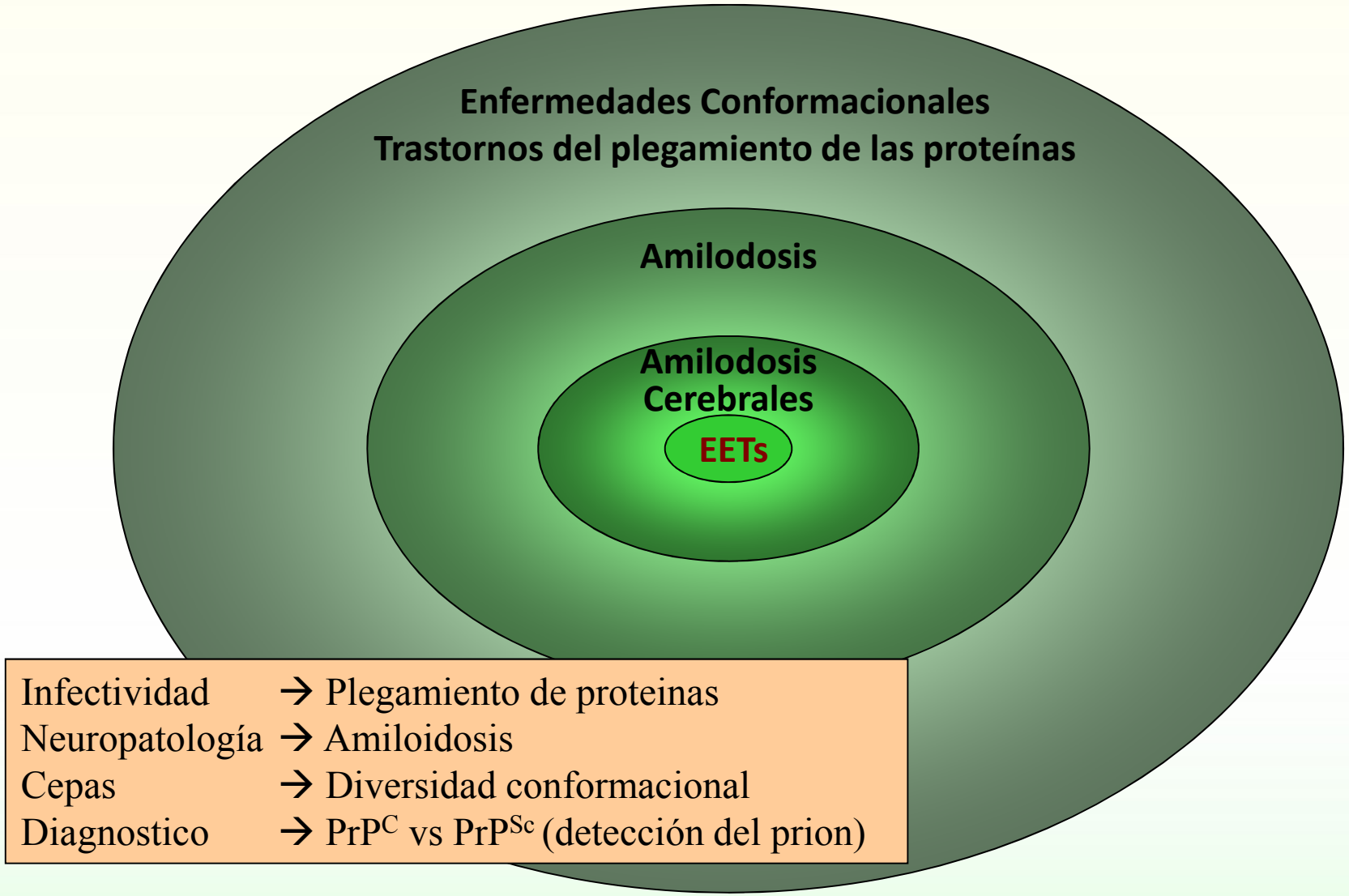
Molecular and cellular basis of NDD

Conformational Disorders (Protein Folding Diseases)



- Not primary aa sequence, nor **function** are key features of these diseases
- Rather, protein instability or tendency to misfold and susceptibility to conformational mimicry

Encefalopatías Espongiformes Transmisibles:
Paradigma de las enfermedades conformacionales



Infectividad	→ Plegamiento de proteinas
Neuropatología	→ Amiloidosis
Cepas	→ Diversidad conformacional
Diagnostico	→ PrP^{C} vs PrP^{Sc} (detección del prion)

Transmissible Spongiform Encephalopathies

Definition. Common Characteristics

A group of fatal neurodegenerative disorders with unique biological properties that affect to both humans and animals

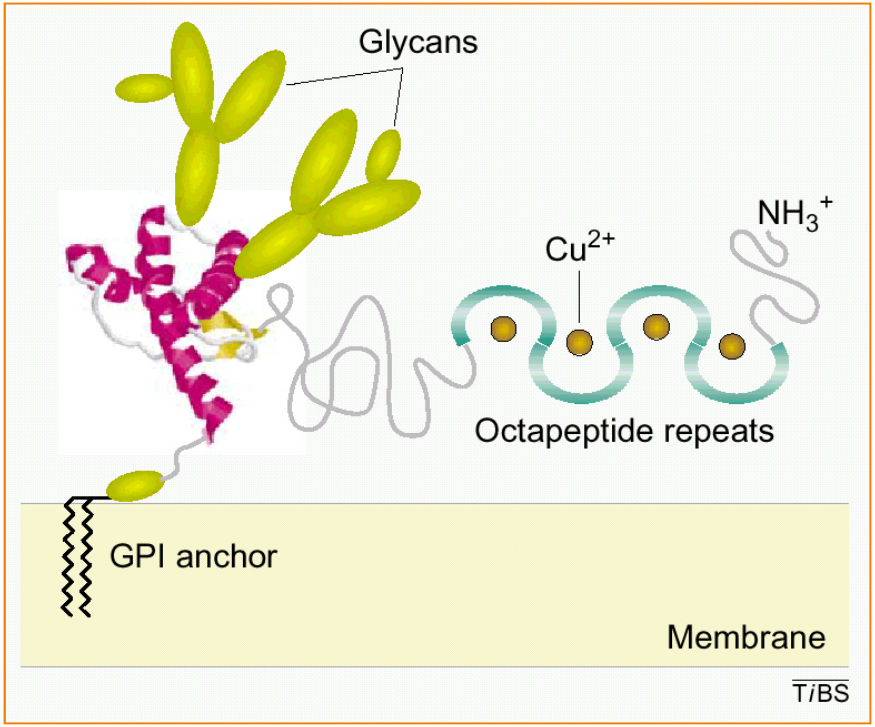
- Long incubation periods
- Neuropathology
- Transmissibility
- **Causal Agent: Prion**

PRIONS
Definition

Prions are proteinaceous infectious particles devoid of nucleic acids

Prions are elements that confer and propagate conformational variability

Protein Structure



Expression

- Central Nervous System
- Lymphatic Tissue
- Neuromuscular connections

Functions

- Synaptic transmission
- Circadian rhythms regulations and the sleep-wake cycles
- Neuronal copper metabolism
- Regulation of Cu^{2+}/Zn^2 Superoxide Dismutase activity
- Oxidative stress and neuronal apoptosis

PRION

Prions are proteinaceous infectious particles devoid of nucleic acids

Transmissibility

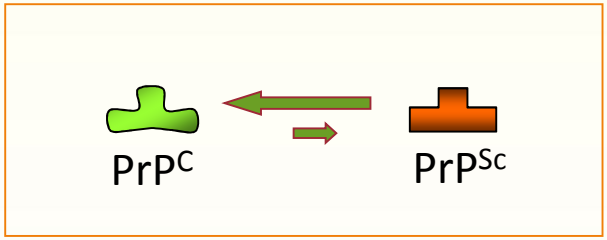
Based on the propagation of the abnormal conformation (PrP^{Sc}) of a constitutively expressed protein (PrP^{c})

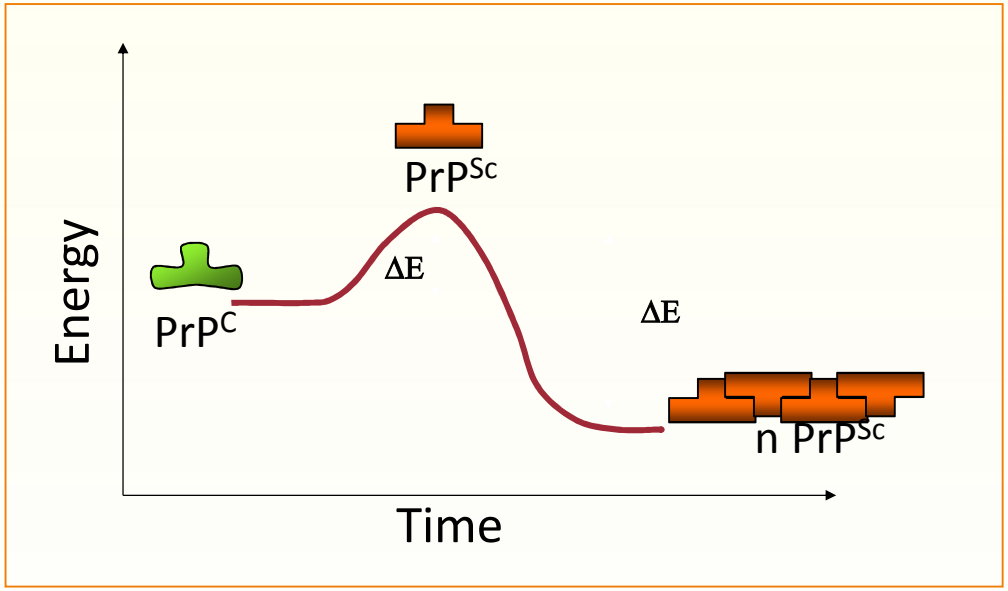
Simultaneously Requires:

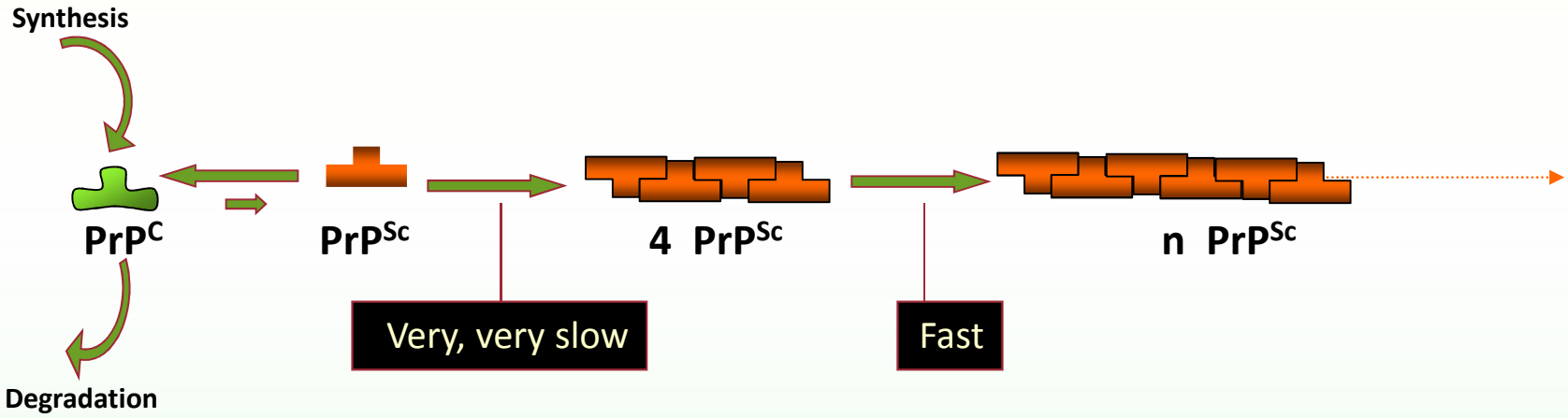
- The presence of the abnormal isoform (PrP^{Sc})
  - Tonsils, lymphoid tissue, spleen
  - Splenic nerve, spinal cord
  - Brain
- *de novo* synthesis of PrP^{c}
  - CNS
  - Lymphoid tissue
  - Neuromuscular conections

Models for PrP^{C} to PrP^{Sc} Conversion

Nucleated polymerization



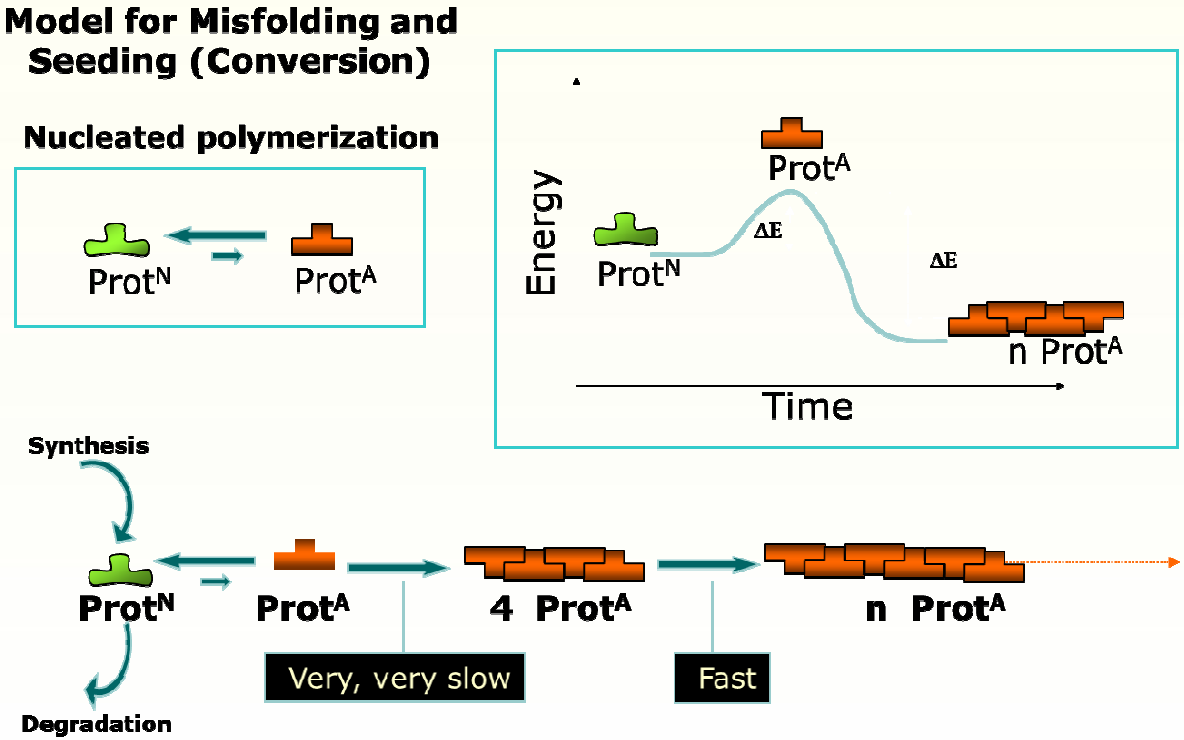




Lansbury PT. Mechanism of scrapie replication. Science. 1994 Sep 9;265(5178):1510.

Molecular and cellular basis of NDD

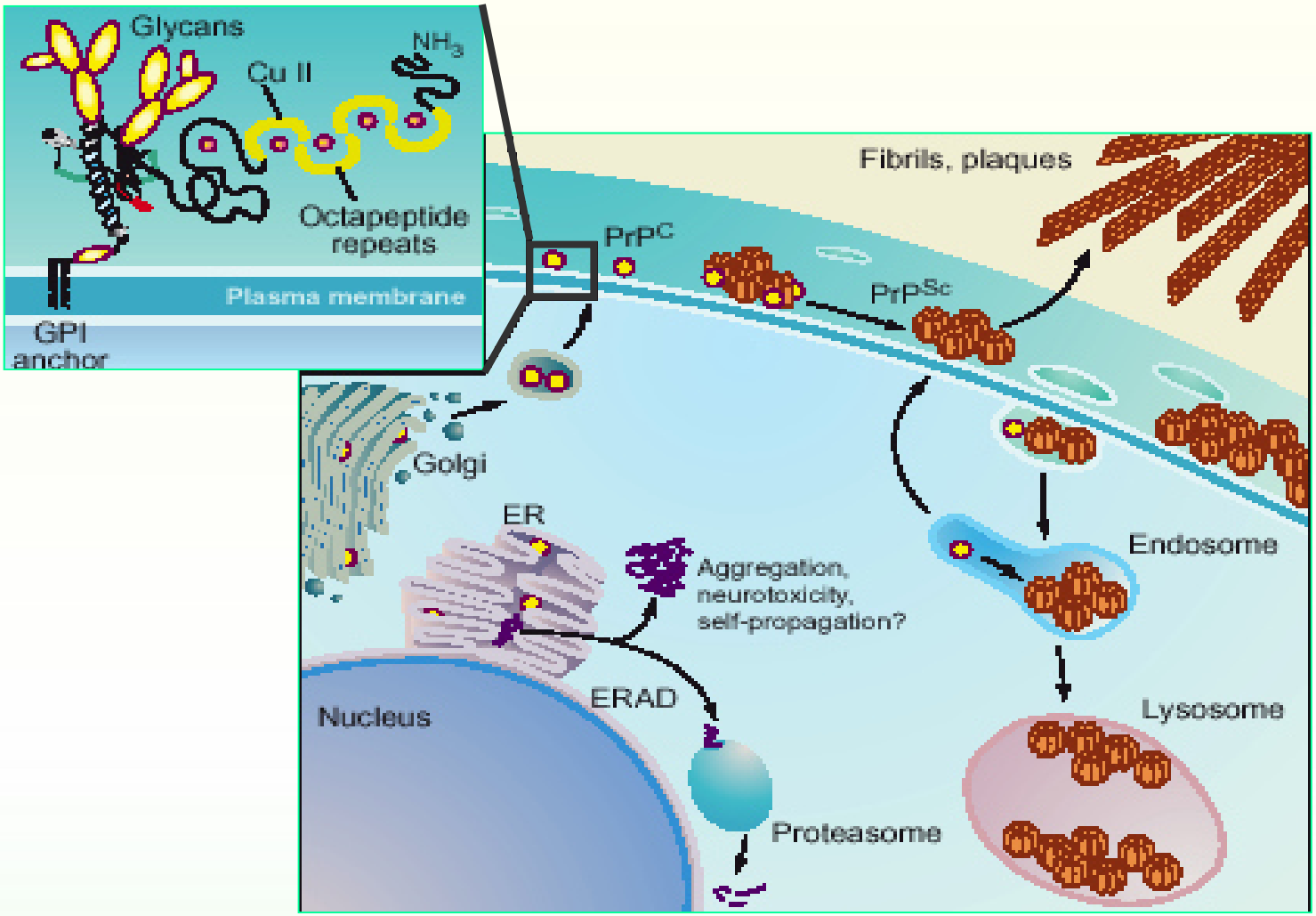
Molecular Transmissibility



Lansbury PT. Mechanism of scrapie replication. Science. 1994 Sep 9;265(5178):1510.

- Etiology: sporadic vs. genetic (vs. infectious)
- Diagnostic implications (Amyloid, tangles: proxies at present → detection of actual pathogen by amplification techniques (RT-QuIC, PMCA)
- Therapeutical implications (disease modifying agents vs. symptomatic treat.)

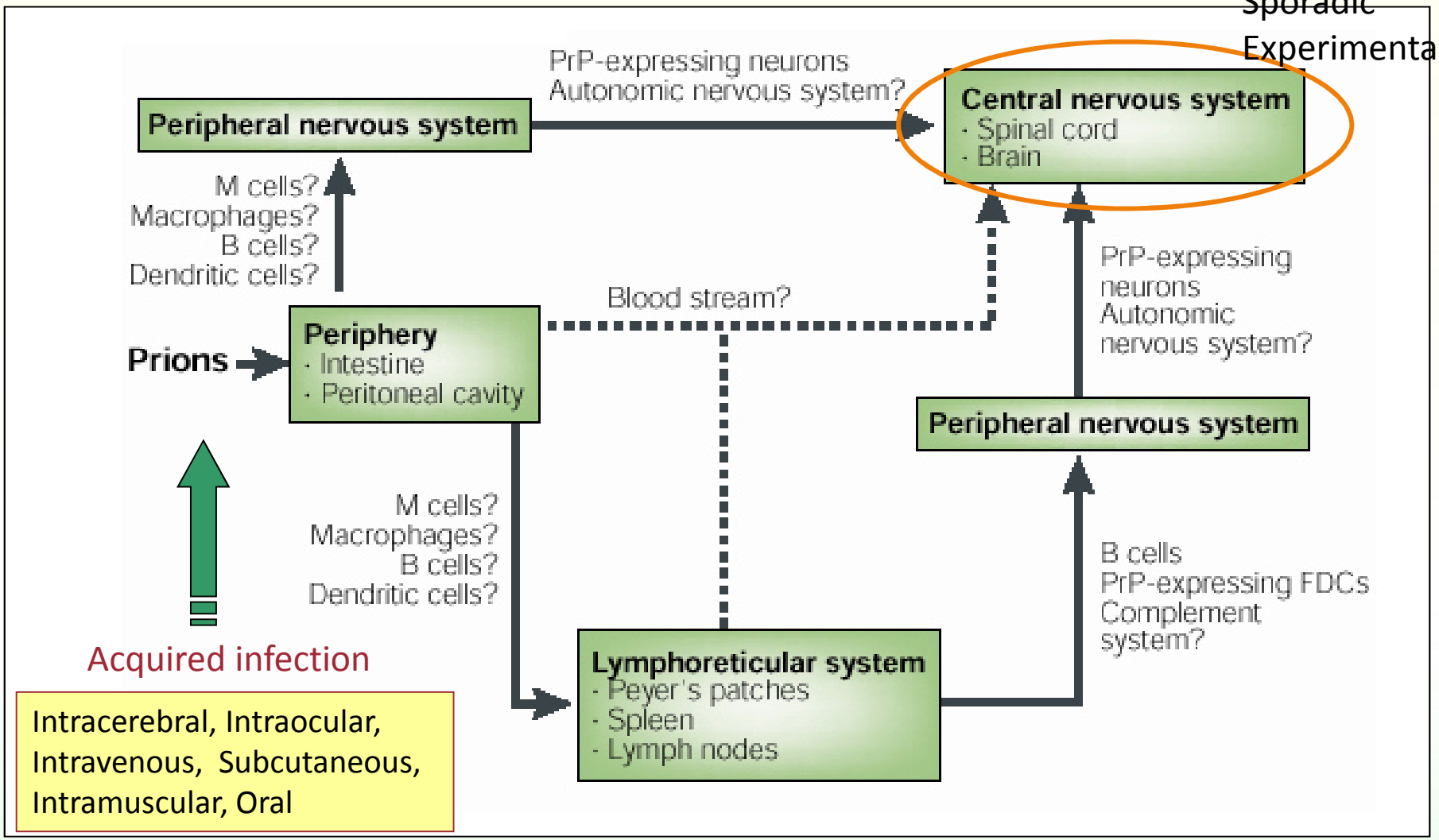
Cellular trafficking of PrP^{C} and PrP^{Sc}



Suzette A.Priola,Bruce Chesebro,Byron Caughey. "A View from the Top. Prion Diseases from 10,000 Feet". *Science* 300, 2003

Model of prion neuroinvasion in mice.

Genetic
Sporadic
Experimental



Nature Reviews Molecular Cell Biology **2, 118 -126 (2001)**

Factores que modulan la transmisión de los priones

Vehículo

Fuente de infección → Huésped

(Inóculo)

Ruta de inoculación

(Intracerebral, Intraocular, Oral, Subcutánea, Intravenosa, Intramuscular)

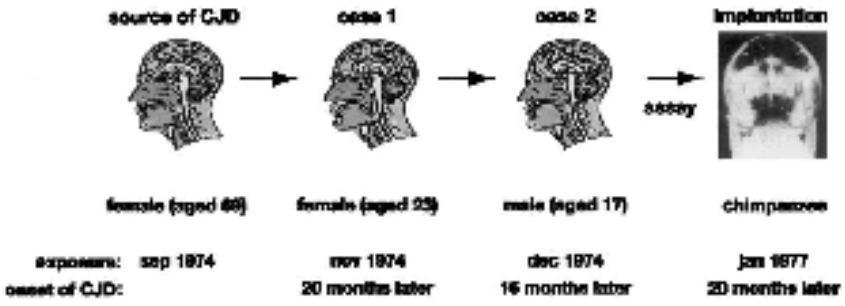
- Dosis y número de exposiciones (tejidos categ de riesgo I, II, III, IV)
- Cepa de prion: ECJe, EEB, vECJ

- Nivel de expresión de PrP^C
- Especie de prion (homología de secuencia con el inóculo)
- Predisposición genética (polimorfismos)
- Otros factores

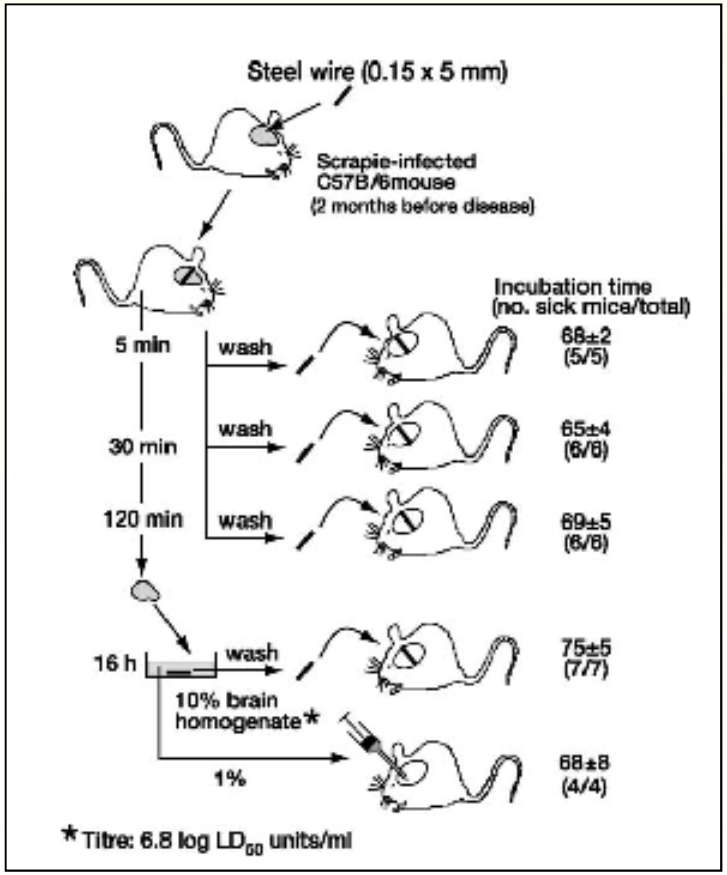
Instrumentos quirúrgicos como vector en las infecciones por priones

ECJ iatrogénica (antecedentes)

Tipo de tratamiento	Número de casos
Hormona de crecimiento	163
Injertos de duramadre	136
Intervenciones neuroquirúrgicas	5
Gonadotrofina hipofisiaria	4
Implante corneal	3
Electrodos esteroatáxicos EEG	2



Weissmann C, Enari M, Klohn PC, Rossi D, Flechsig E. Transmission of prions. Proc Natl Acad Sci U S A. 99:16378-83. 2002



Cirugía

Transplante de órganos

Transfusión sanguínea (vCJD)

BEYOND THE PRION PRINCIPLE

ARTICLE

Received 8 May 2014 | Accepted 9 Jun 2014 | Published 9 Jul 2014

DOI: 10.1038/ncomms5347 OPEN

Prion neuropathology follows the accumulation of alternate prion protein isoforms after infective titre has peaked

Malin K. Sandberg[1], Huda Al-Doujaily[1], Bernadette Sharps[1], Michael Wiggins De Oliveira[1], Christian Schmidt[1], Angela Richard-Londt[1], Sarah Lyall[1], Jacqueline M. Linehan[1], Sebastian Brandner[1], Jonathan D.F. Wadsworth[1], Anthony R. Clarke[1] & John Collinge[1]

Prions are lethal infectious agents thought to consist of multi-chain forms (PrP^{Sc}) of misfolded cellular prion protein (PrP^{C}). Prion propagation proceeds in two distinct mechanistic phases: an exponential phase 1, which rapidly reaches a fixed level of infectivity irrespective of PrP^{C} expression level, and a plateau (phase 2), which continues until clinical onset with duration inversely proportional to PrP^{C} expression level. We hypothesized that neurotoxicity relates to distinct neurotoxic species produced following a pathway switch when prion levels saturate. Here we show a linear increase of proteinase K-sensitive PrP isoforms distinct from classical PrP^{Sc} at a rate proportional to PrP^{C} concentration, commencing at the phase transition and rising until clinical onset. The unaltered level of total PrP during phase 1, when prion infectivity increases a million-fold, indicates that prions comprise a small minority of total PrP. This is consistent with PrP^{C} concentration not being rate limiting to exponential prion propagation and neurotoxicity relating to critical concentrations of alternate PrP isoforms whose production is PrP^{C} concentration dependent.

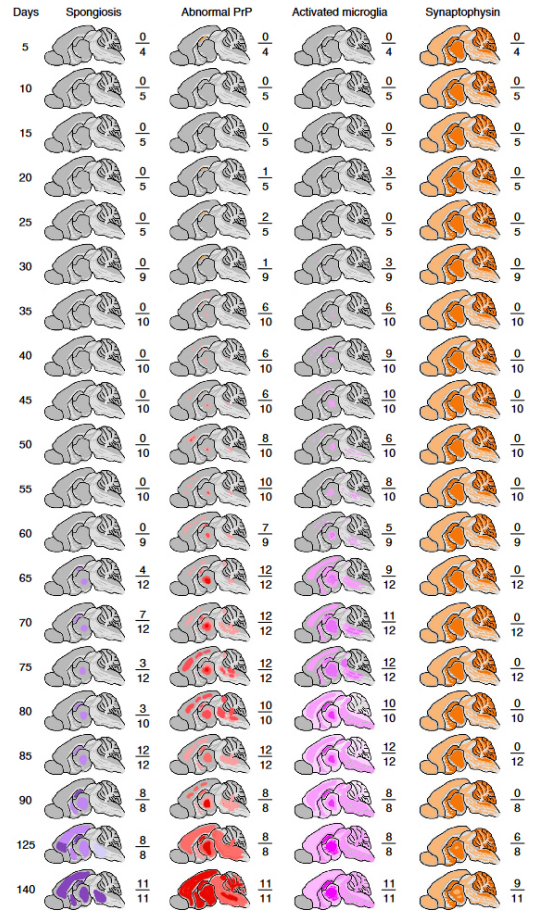


Figure 5 | Evolution of pathological changes in the brain during prion infection. FVB/N mice were intracerebrally inoculated with RML prions and groups of mice culled at defined time points or at onset of clinical prion disease. The mean incubation period was 168 ± 2.5 days (± s.d.). Fixed brains from each timed cull were analysed for spongiform change by haematoxylin and eosin (H&E) staining together with immunohistochemical analyses for abnormal PrP deposition, microglia activation and neuronal loss (monitored by synaptophysin staining). Schematic representations of the brain taken at various time points show the evolution of pathological changes throughout the disease course. Numbers shown next to the schematics report the number of animals in the group positive for the pathology shown as a fraction of the total number of animals in each group.

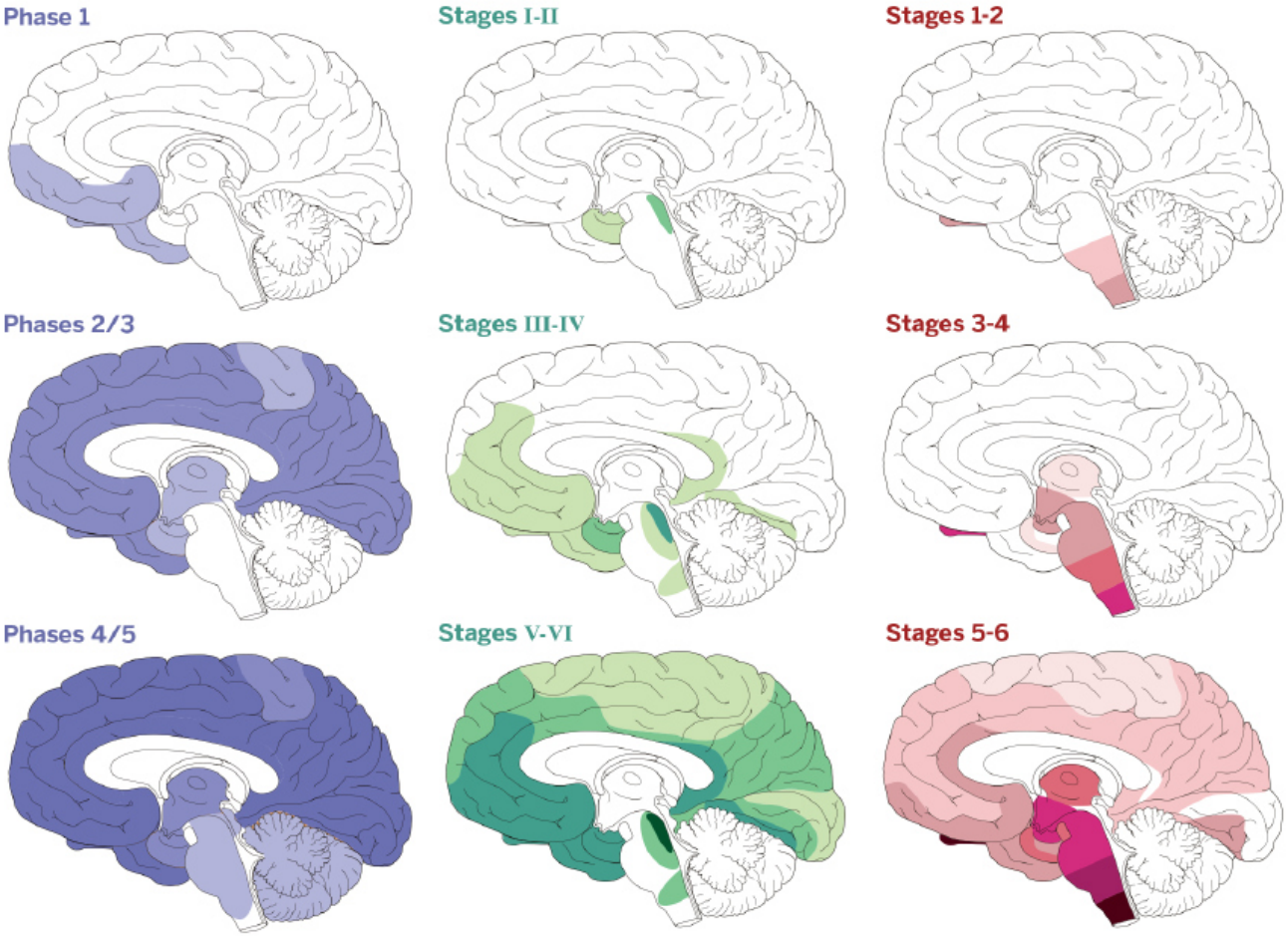
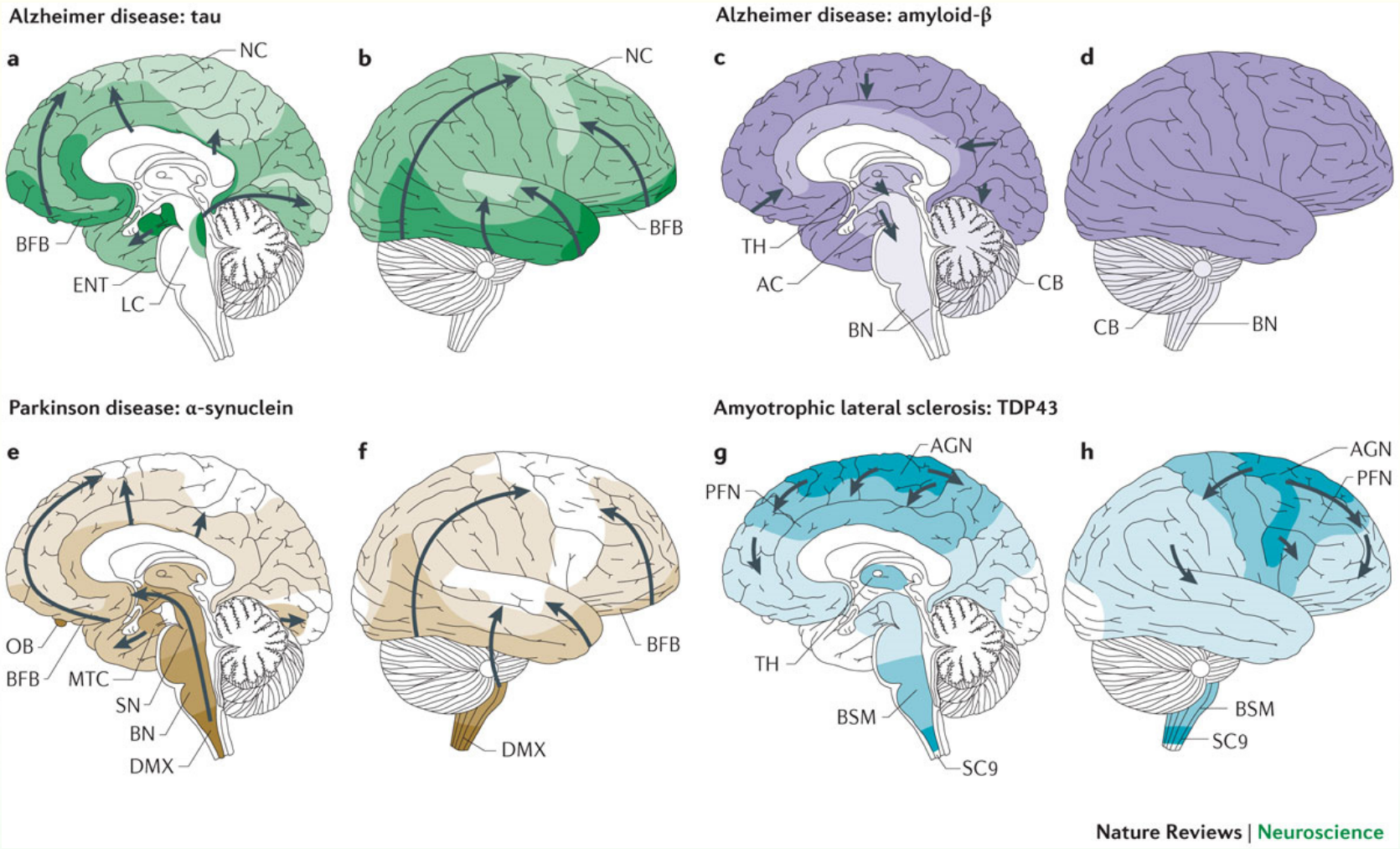


Fig. 3. Propagation of Aβ, tau, and α-synuclein inclusions in human brain. (**Left**) (Blue) Aβ plaques develop first in one or more sites in the basal temporal and orbitofrontal neocortex (phase 1). They are observed later throughout the neocortex, in hippocampal formation, amygdala, diencephalon, and basal ganglia (phases 2 and 3). In severe cases of AD, Aβ plaques are also found in mesencephalon, lower brainstem, and cerebellar cortex (phases 4 and 5). (**Middle**) (Green) Tau inclusions develop in the locus coeruleus, as well as in the transentorhinal and entorhinal regions (stages I and II). This is followed by the presence of tau inclusions in the hippocampal formation and some parts of the neocortex (stages III and IV), followed by large parts of the neocortex (stages V and VI). (**Right**) (Red) α-Synuclein-positive Lewy pathology ascends from the brainstem. The first inclusions are present in the olfactory bulb and the dorsal motor nucleus of the vagal and glossopharyngeal nerves of the medulla oblongata (stages 1 and 2). From the brainstem, the pathology spreads through the pons to midbrain and basal forebrain (stages 3 and 4), followed by the neocortex (stages 5 and 6). [Fig. 3 is based on the work of H. Braak, K. Del Tredici, and collaborators. Adapted, with permission, from (*9*, *64*)]

Michel Goedert. SCIENCE sciencemag.org 7 AUGUST 2015 • VOL 349 ISSUE 6248

Sequential topographical dissemination of non-prion proteins in neurodegenerative diseases



From Spreading of pathology in neurodegenerative diseases: a focus on human studies. Johannes Brettschneider, Kelly Del Tredici, Virginia M.-Y. Lee & John Q. Trojanowski. Nature Reviews Neuroscience 16, 109–120 (2015).

OXFORD

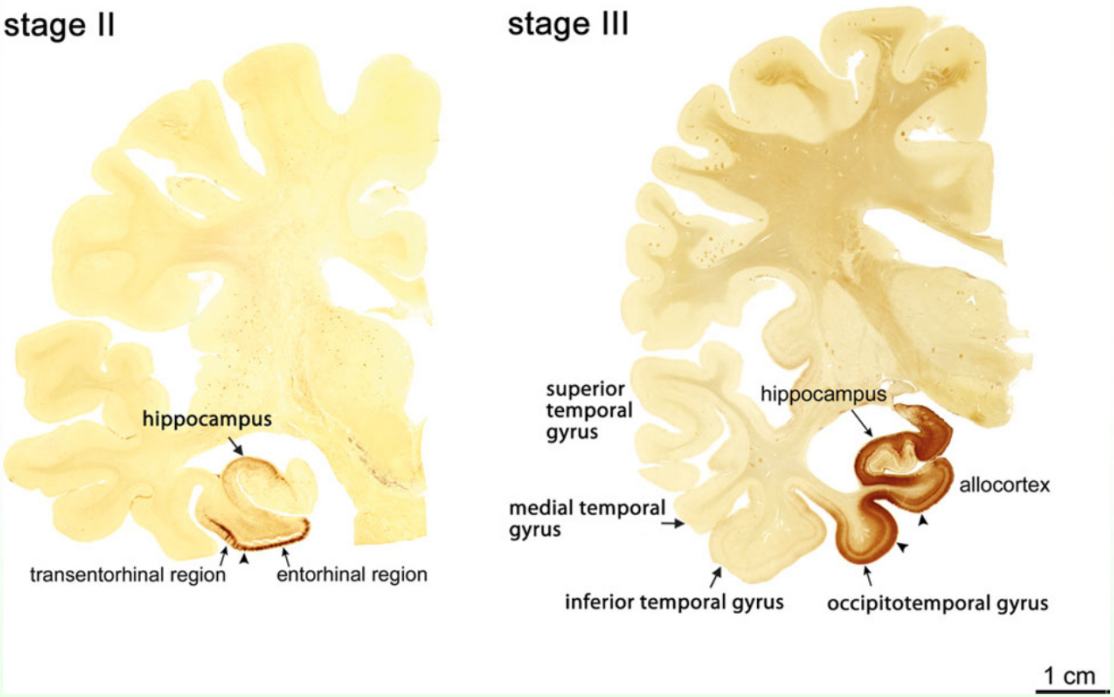
Cerebral Cortex, September 2018;28: 3372–3384

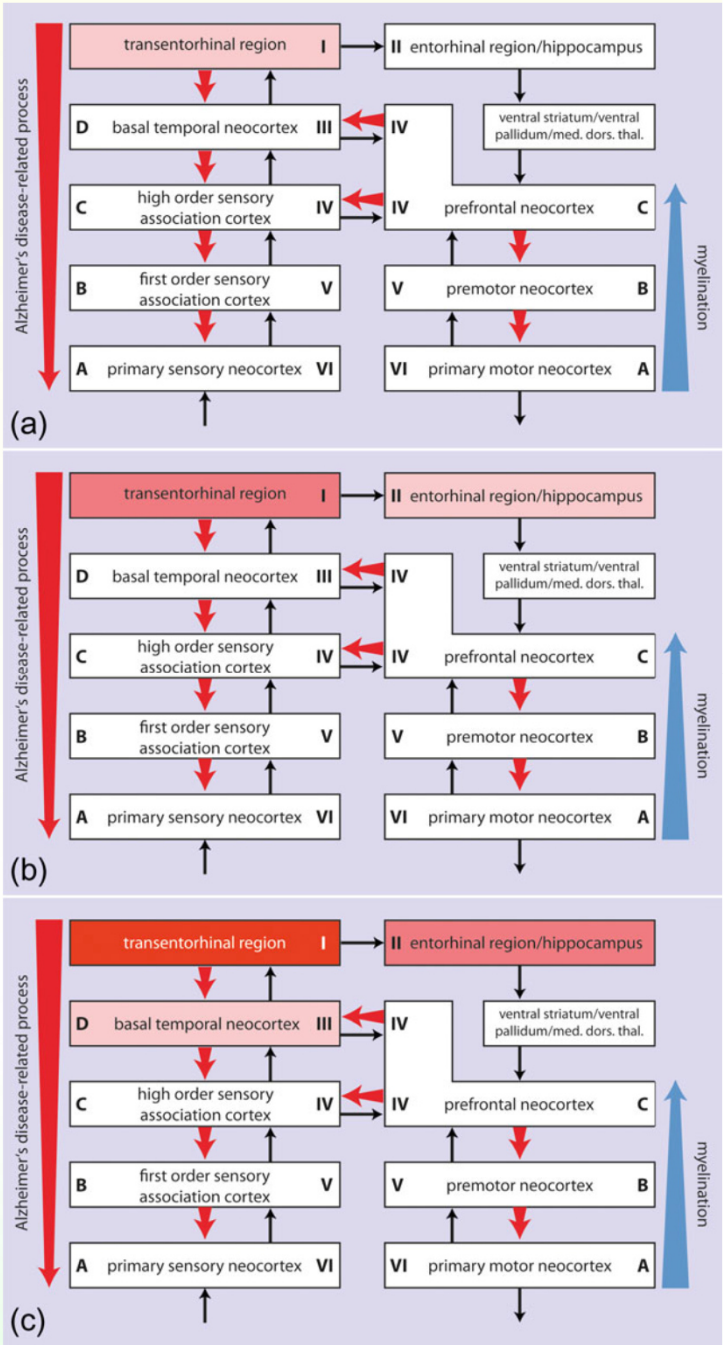
doi: 10.1093/cercor/bhy152
Advance Access Publication Date: 30 June 2018
Original Article

ORIGINAL ARTICLE

Spreading of Tau Pathology in Sporadic Alzheimer's Disease Along Cortico-cortical Top-Down Connections

Heiko Braak and Kelly Del Tredici

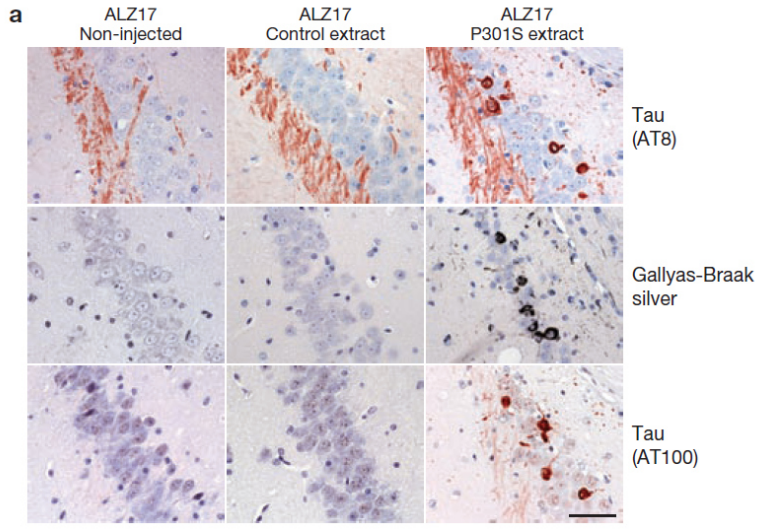


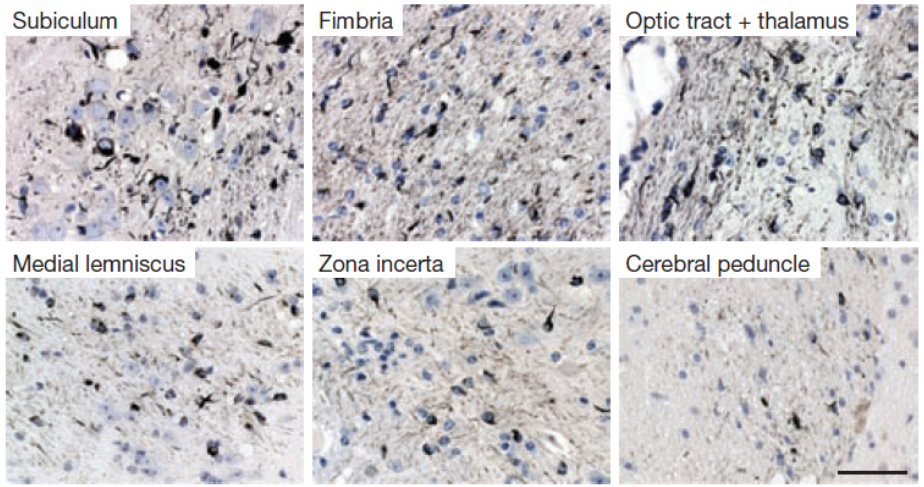


nature
cell biology

Transmission and spreading of tauopathy in transgenic mouse brain

Florence Clavaguera[1], Tristan Bolmont[2], R. Anthony Crowther[3], Dorothee Abramowski[4], Stephan Frank[1], Alphonse Probst[1], Graham Fraser[3], Anna K. Stalder[5], Martin Beibel[4], Matthias Staufenbiel[4], Mathias Jucker[2], Michel Goedert[3,6,7] and Markus Tolnay[1,6,7]





Nat Cell Biol. 2009 Jul;11(7):909-13.

ORIGINAL ARTICLE

De novo induction of amyloid-β deposition *in vivo*

R Morales[1,2], C Duran-Aniotz[1,3], J Castilla[2,4], LD Estrada[2,5] and C Soto[1,2]

[1]*Mitchell Center for Alzheimer's Disease and Related Brain Disorders, Department of Neurology, University of Texas Houston Medical School, Houston, TX, USA;* [2]*University of Texas Medical Branch at Galveston, Galveston, TX, USA;* [3]*Universidad de Los Andes, Facultad de Medicina. Av. San Carlos de Apoquindo 2200, Las Condes, Santiago, Chile and* [4]*CIC bioGUNE, Parque Tecnologico de Biskaia, Ed 800, 48160 Derio and IKERBASQUE, Basque Foundation for Science, 48011 Bilbao, Spain*

Molecular Psychiatry (2011), 1–7

www.nature.com/mp

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PLoS one

Trans-Synaptic Spread of Tau Pathology *In Vivo*

Li Liu[1], Valerie Drouet[1], Jessica W. Wu[1], Menno P. Witter[2], Scott A. Small[3], Catherine Clelland[1], Karen Duff[1,4]*

1 Department of Pathology and Cell Biology, Taub Institute for Alzheimer's Disease Research, Columbia University, New York, New York, United States of America, **2** Kavli Institute for Systems Neuroscience and Centre for the Biology of Memory, Norwegian University of Science and Technology, Trondheim, Norway, **3** Department of Neurology, Taub Institute for Alzheimer's Disease Research, Columbia University, New York, New York, United States of America, **4** Department of Psychiatry, New York State Psychiatric Institute, New York, New York, United States of America

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CELL BIOLOGY

Beyond the prion principle

Adriano Aguzzi

It seems that many misfolded proteins can act like prions — spreading disease by imparting their misshapen structure to normal cellular counterparts. But how common are bona fide prions really?

NATURE|Vol 459|18 June 2009

PRIONS AND POTENTIAL PRIONOIDS

Disease	Protein	Molecular transmissibility	Infectious life cycle
Prion diseases	PrP^{Sc}	Yes	Yes
Alzheimer's disease	Amyloid-β	Yes	Not shown
Tauopathies	Tau	Yes	Not shown
Parkinson's disease	α-Synuclein	Host-to-graft	Not shown
AA amyloidosis	Amyloid A	Yes	Possible
Huntington's disease	Polyglutamine	Yes	Not shown

Phenotype	Protein	Molecular transmissibility	Infectious life cycle
Suppressed translational termination (yeast)	Sup35	Yes	Not shown
Heterokaryon incompatibility (filamentous fungi)	Het-s	Yes	Not shown
Biofilm promotion (bacteria)	CsgA	Yes	Not shown

In humans and animals, infectious prion diseases are caused by PrP^{Sc}, which spreads by recruiting its monomeric precursor PrP^{C} into aggregates. Aggregates then multiply by breakage, a process that is termed molecular transmissibility. Other proteins involved in disease and in phenotypes of fungi and bacteria, can also undergo self-sustaining aggregation, but none of these 'prionoid' proteins behaves like typical infectious agents, nor do any of them enact a complete infectious life cycle — with the possible exception of AA amyloid.

Neuron
Perspective

The Transcellular Spread of Cytosolic Amyloids, Prions, and Prionoids

Adriano Aguzzi[1,*] and Lawrence Rajendran[2,*]
[1]Institute of Neuropathology, University Hospital of Zürich, Schmelzbergstrasse 12, CH-8091 Zürich, Switzerland
[2]Systems and Cell Biology of Neurodegeneration, Psychiatry Research, University of Zurich, CH-8008 Zürich, Switzerland
*Correspondence: adriano.aguzzi@usz.ch (A.A.), rajendran@bli.uzh.ch (L.R.)
DOI 10.1016/j.neuron.2009.12.016

Recent reports indicate that a growing number of intracellular proteins are not only prone to pathological aggregation but can also be released and "infect" neighboring cells. Therefore, many complex diseases may obey a simple model of propagation where the penetration of seeds into hosts determines spatial spread and disease progression. We term these proteins *prionoids*, as they appear to infect their neighbors just like prions—but how can bulky protein aggregates be released from cells and how do they access other cells? The widespread existence of such prionoids raises unexpected issues that question our understanding of basic cell biology.

Table 1. Potential Prionoids in Health and Disease (Adapted from Aguzzi, 2009)

Phenotype/Function	Protein	Molecular Transmissibility	Bona Fide Infectivity
Prion diseases	PrP^{Sc} (luminal)	yes	yes
Alzheimer's disease	Aβ (luminal)	yes	in APP-overexpressing mice
Tauopathies	Tau (cytosolic)	possibly	not shown
Parkinson's disease	α-synuclein (cytosolic)	host-to-graft	not shown
AA amyloidosis	SAA (luminal)	yes	probable
Huntington's disease	PolyQ (nuclear)	yes	not shown
Suppressed translational termination (yeast)	Sup35	yes	limited
Biofilm production (bacteria)	bacterial curlin	yes	questionable
Heterkaryon incompatibility (fungi)	Het-s	yes	limited
Pituitary secretory granules	peptide hormones	not shown	not shown
Mammalian skin pigmentation	Pmel17	not shown	not shown

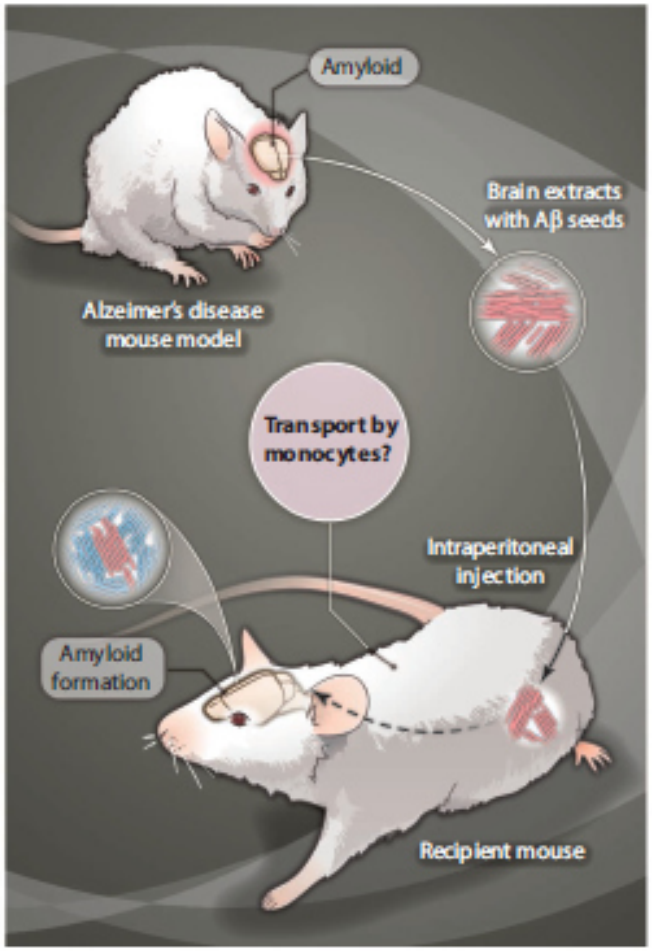
MEDICINE

Prion-Like Behavior of Amyloid-β

Can Alzheimer's disease arise through pathogenic transmission of a protein aggregate?

Jungsu Kim and David M. Holtzman

Can certain neurodegenerative diseases be transmitted between humans by an infectious agent? The discovery that protein particles called prions can enter healthy mammals, including humans, and trigger a cascade of endogenous protein misfolding associated with bovine spongiform encephalopathy ("mad cow disease") and Creutzfeldt-Jakob disease, certainly demonstrates this in prion diseases. Remarkably, neuronal proteins such as tau, α-synuclein, and polyglutamine aggregates, which are causally implicated in the neurodegenerative disorders Alzheimer's disease, Parkinson's disease, and Huntington's disease, respectively, can be released from donor cells and taken up by neighboring acceptor cells. Moreover, treatment with exogenous misfolded neuronal proteins, such as tau, can trigger the misfolding and aggregation of their properly



Amyloid transmission. Injection of mouse brain extract containing

protein denaturation and specific immunodepletion of Aβ (*6*). Yet systemic administration of Aβ-containing brain lysates, either orally or by intravenous, intraocular, or intranasal injection, failed to induce cerebral Aβ amyloidosis in mice (*7*).

Surprisingly, Eisele *et al*. show that intraperitoneal injection of mice with mouse brain extracts containing Aβ aggregates leads to earlier-onset amyloid deposition and other pathological alterations in recipient mice (5 months after exposure) (see the figure). Aβ aggregates were predominantly associated with cerebral blood vessels, and amyloidosis was associated with local gliosis (proliferation of glia in damaged areas) and hyperphosphorylation of tau protein, the major component of neurofibrillary tangles. Thus, cerebral amyloidosis can be induced in a susceptible host by Aβ-containing material delivered outside the brain. It is unclear why the previous attempts with intravenous injection failed to trigger Aβ deposition. It is possible that other modes of administration could induce amyloidosis if the incubation time of the injected seed is sufficiently long and if the seed has a proper conformation.

The transmission mechanism by which the peripherally injected amyloid-inducing factor penetrates into the brain is also not clear.

SCIENCE 330, pg 918-9. 12 NOVEMBER 2010 (www.sciencemag.org)

Early Onset Cerebral Amyloid Angiopathy following Childhood Exposure to Cadaveric Dura

Gargi Banerjee, MRCP,[1]
Matthew E. Adams, FRCR,[2]
Zane Jaunmuktane, FRCPath,[3,4]
G. Alistair Lammie, FRCPath,[5]
Ben Turner, MD,[6] Mushtaq Wani, FRCP,[7]
Inder M. S. Sawhney, DM,[7]
Henry Houlden, PhD,[3] Simon Mead, PhD,[8,9]
Sebastian Brandner, MD, FRCPath,[4,10] and
David J. Werring, FRCP[1]

Amyloid-β transmission has been described in patients both with and without iatrogenic Creutzfeldt–Jakob disease; however, there is little information regarding the clinical impact of this acquired amyloid-β pathology during life. Here, for the first time, we describe in detail the clinical and neuroimaging findings in 3 patients with early onset symptomatic amyloid-β cerebral amyloid angiopathy following childhood exposure to cadaveric dura (by neurosurgical grafting in 2 patients and tumor embolization in a third). Our observations provide further in vivo evidence that cerebral amyloid angiopathy might be caused by transmission of amyloid-β seeds (prions) present in cadaveric dura and have diagnostic relevance for younger patients presenting with suspected cerebral amyloid angiopathy.

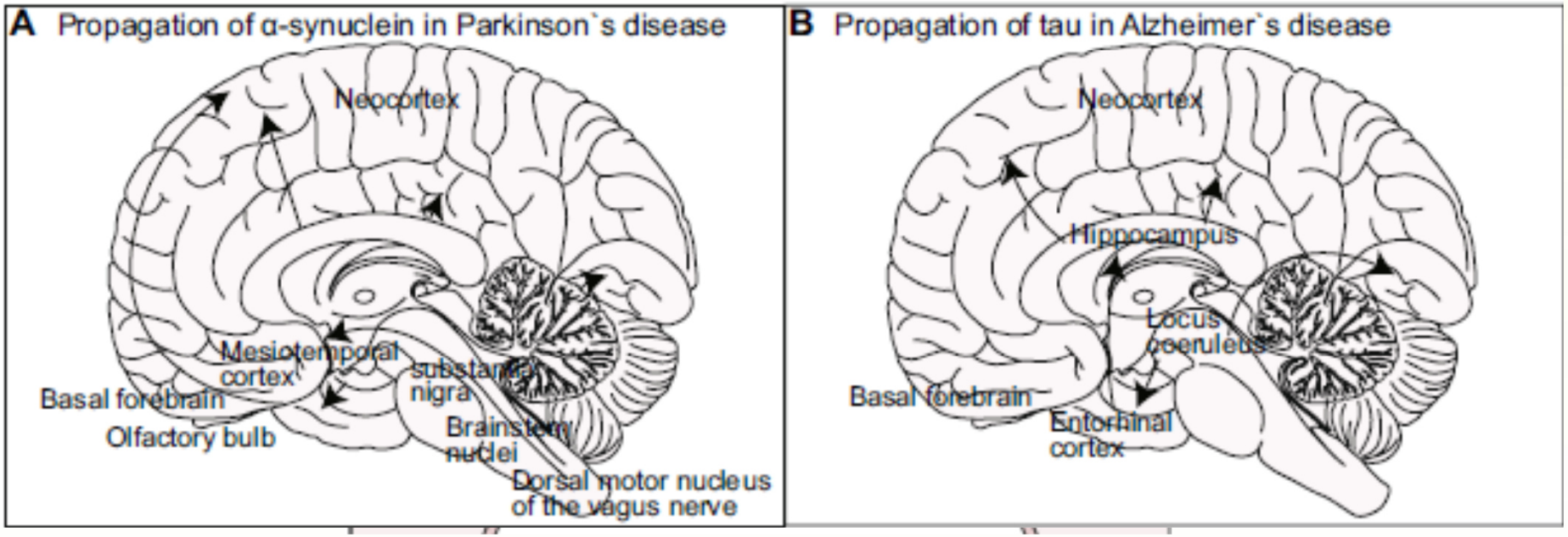
ANN NEUROL 2019;85:284–290

- Three people with early onset CAA received dural grafts from cadavers as children.
- In one case, the dural material was confined to blood vessels.
- Data provides more evidence for transmission of Aβ seeds, even from blood to brain.

https://www.alzforum.org/news/research-news/first-vivo-look-amyloidosis-sparked-dural-grafts

Molecular and cellular basis of NDD

Cellular susceptibility and intercellular transmission



Propagation of misfolded proteins via intercellular transmission

- Therapeutical implications (disease modifying agents vs. symptomatic treat.)

Chung CG, Lee H, Lee SB. Mechanisms of protein toxicity in neurodegenerative diseases. Cellular and Molecular Life Sciences. 2018 Sep;75(17):3159–80.

Molecular and cellular basis of NDD

Molecular Nexopathies

Specific, coherent conjunctions of **pathogenic protein** and **intrinsic network characteristics** that define network signatures of **neurodegenerative pathologies**.

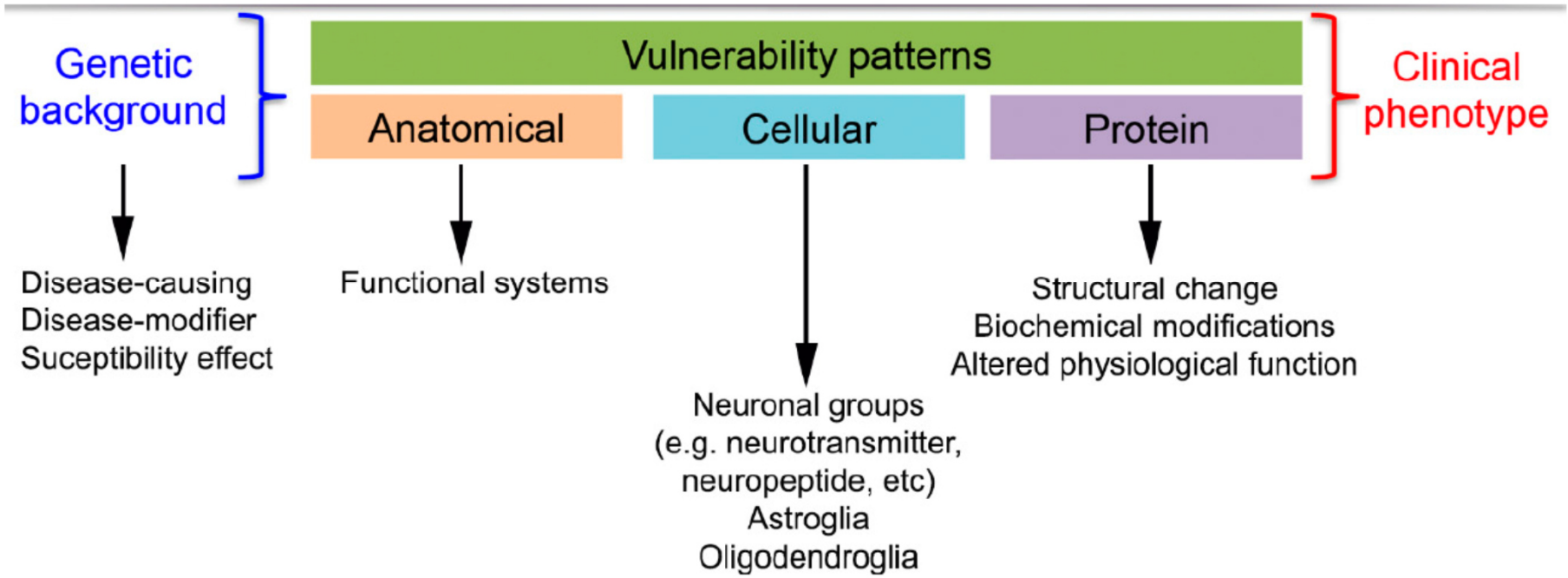
Key Features

- **differential intrinsic network vulnerability** to propagating protein abnormalities, in part reflecting developmental structural and functional factors;
- **differential vulnerability** of neural connection types (e.g., clustered versus distributed connections) to **particular pathogenic proteins**;
- **differential impact of molecular effects** (e.g., toxic-gain-of-function versus loss-of-function) on gradients of network damage.

Molecular nexopathies: a new paradigm of neurodegenerative disease. Warren JD, Rohrer JD, Schott JM, Fox NC, Hardy J, Rossor MN. Trends Neurosci. 2013 Oct;36(10):561-9. doi: 10.1016/j.tins.2013.06.007.

Clinico-pathological presentation of NND

Vulnerability patterns



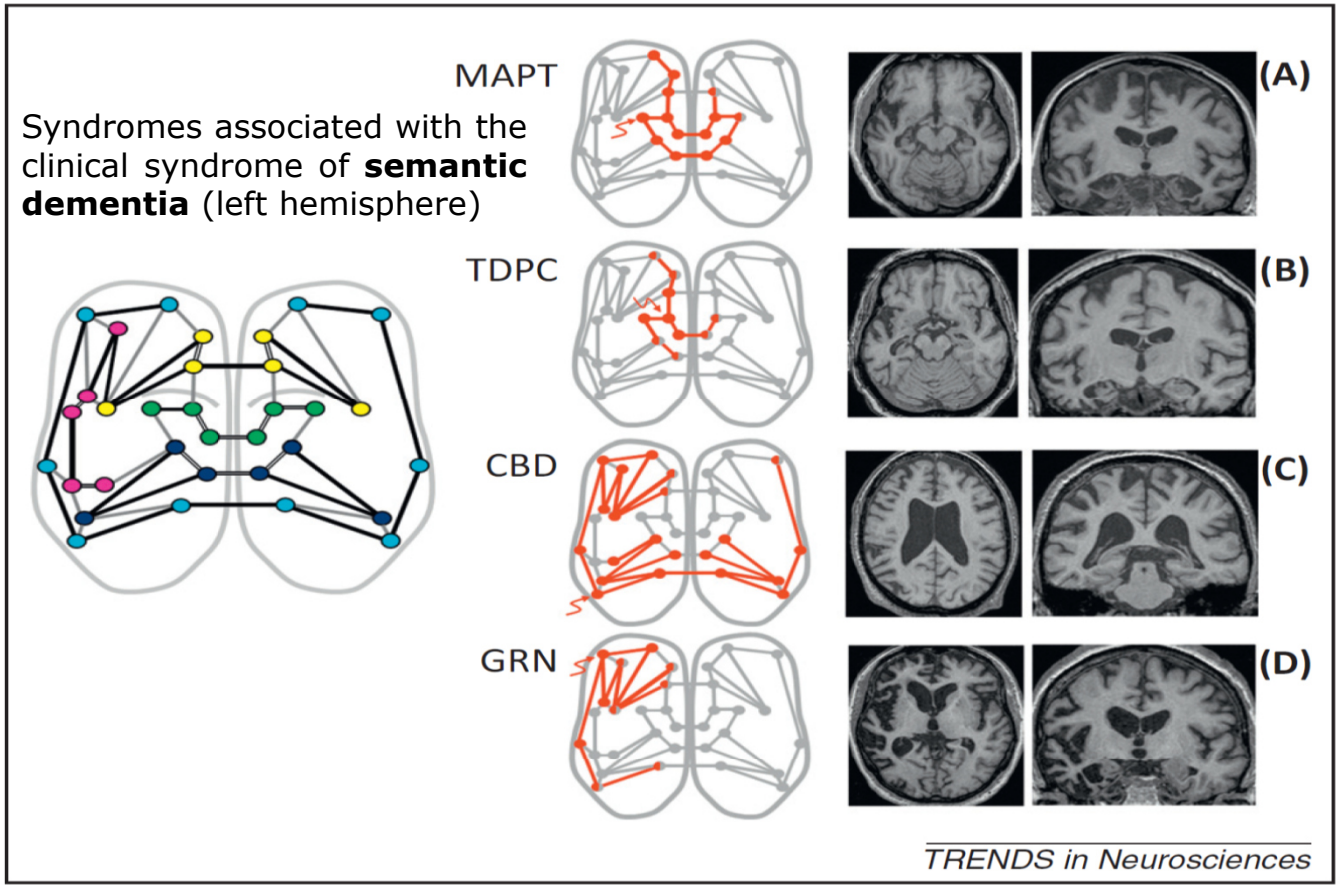
Concept of vulnerability patterns in neurodegenerative diseases

Molecular Pathological Classification of Neurodegenerative Diseases: Turning towards Precision Medicine. Kovacs GG. Int J Mol Sci. 2016 Feb 2;17(2). pii: E189. doi: 10.3390/ijms17020189.

Molecular and cellular basis of NDD

Molecular Nexopathies

Networks show variable intrinsic vulnerability to proteinopathies



mutation in *MAPT* (tau) gene

TDP-43 type C pathology

corticobasal degeneration (4R-tau pathology)

mutation in progranulin gene

Figure 2. Scaling nexopathies to large-scale brain networks. The inset cartoon

Molecular nexopathies: a new paradigm of neurodegenerative disease. Warren JD, Rohrer JD, Schott JM, Fox NC, Hardy J, Rossor MN. Trends Neurosci. 2013 Oct;36(10):561-9. doi: 10.1016/j.tins.2013.06.007.

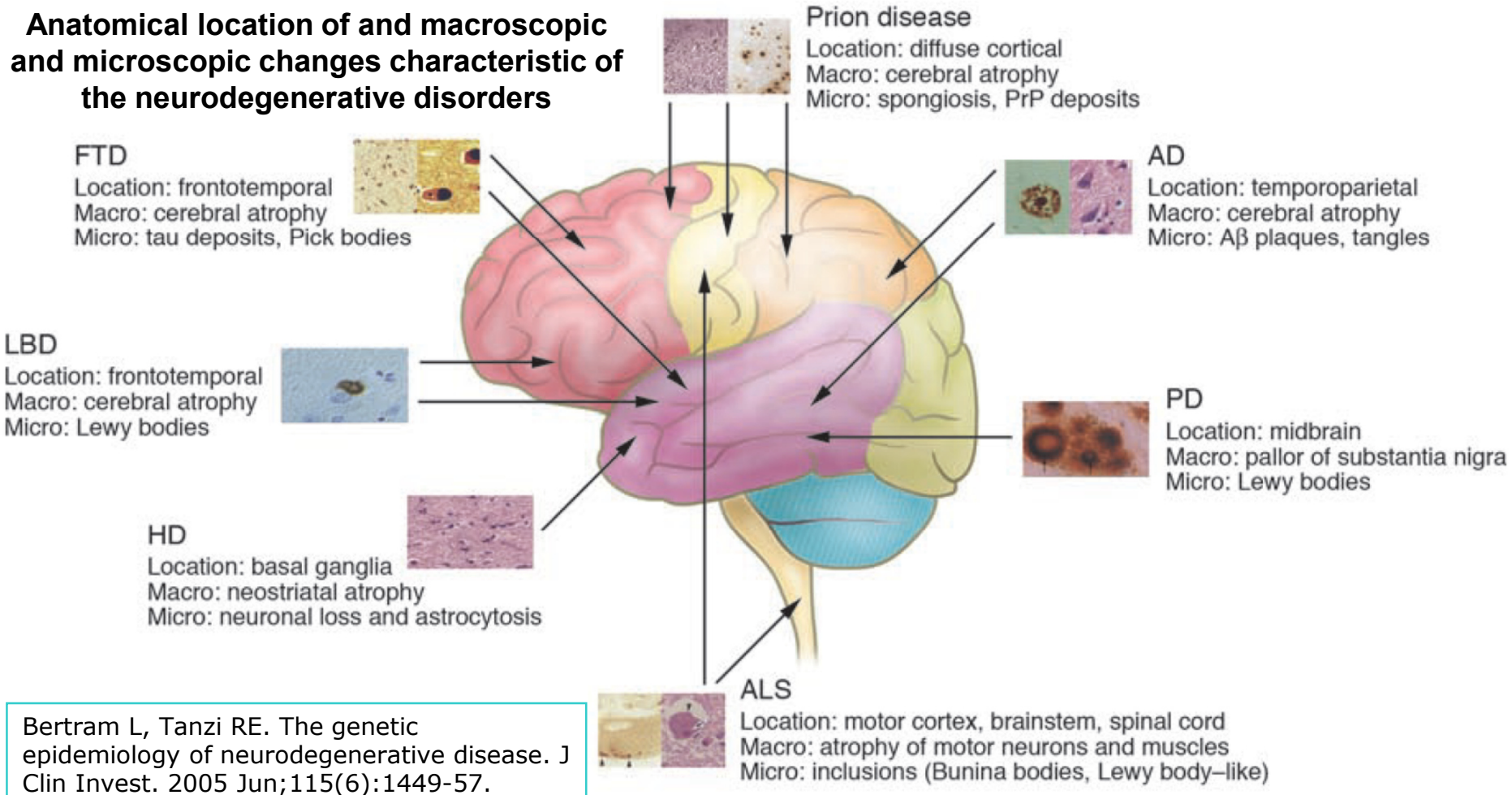
Clinico-pathological presentation of NND

Clinical presentation

→ Brain regions affected (initial stages)

→ Dementias and Motor disorders

Anatomical location of and macroscopic and microscopic changes characteristic of the neurodegenerative disorders

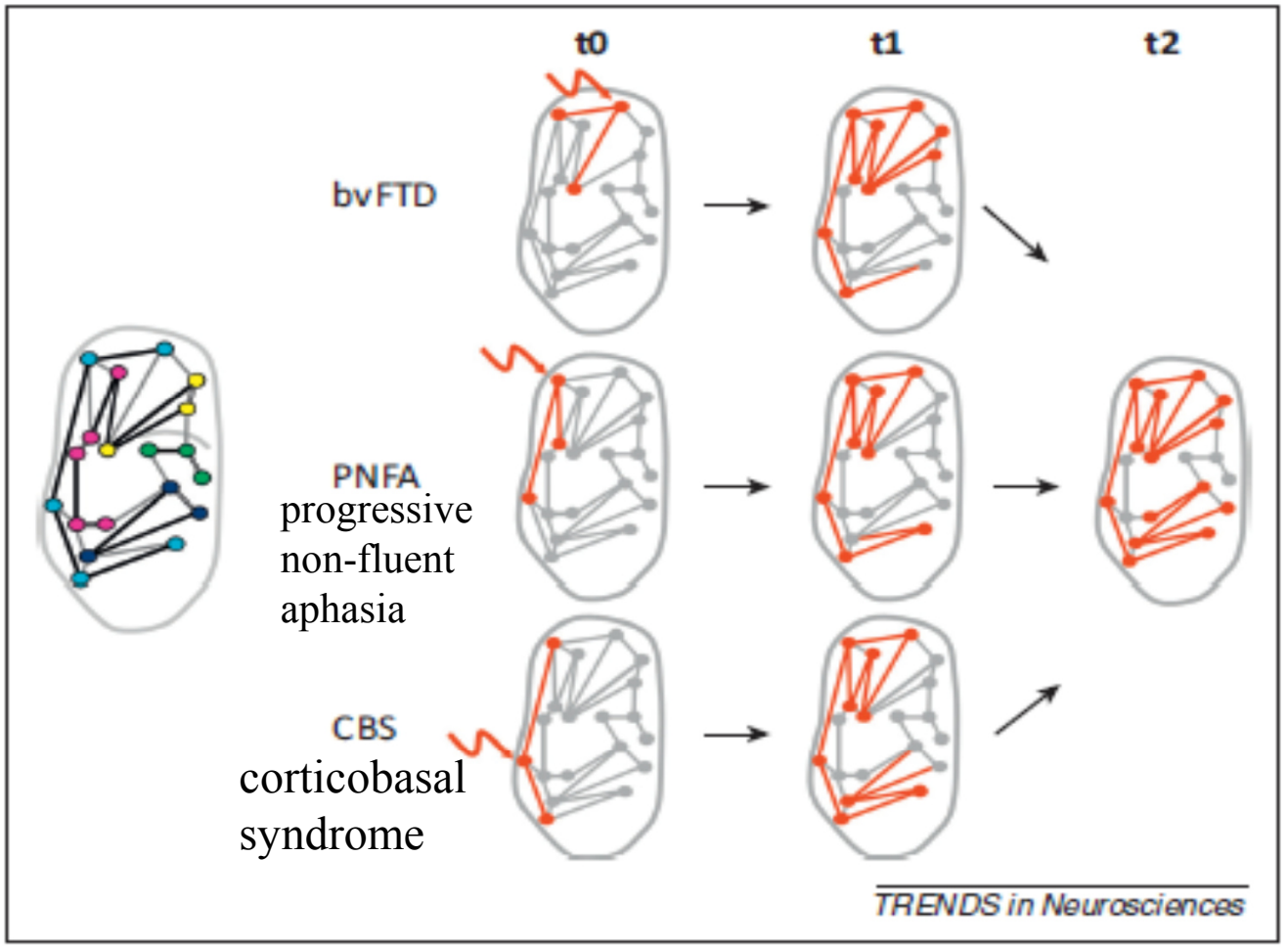


Bertram L, Tanzi RE. The genetic epidemiology of neurodegenerative disease. J Clin Invest. 2005 Jun;115(6):1449-57.

Molecular and cellular basis of NDD

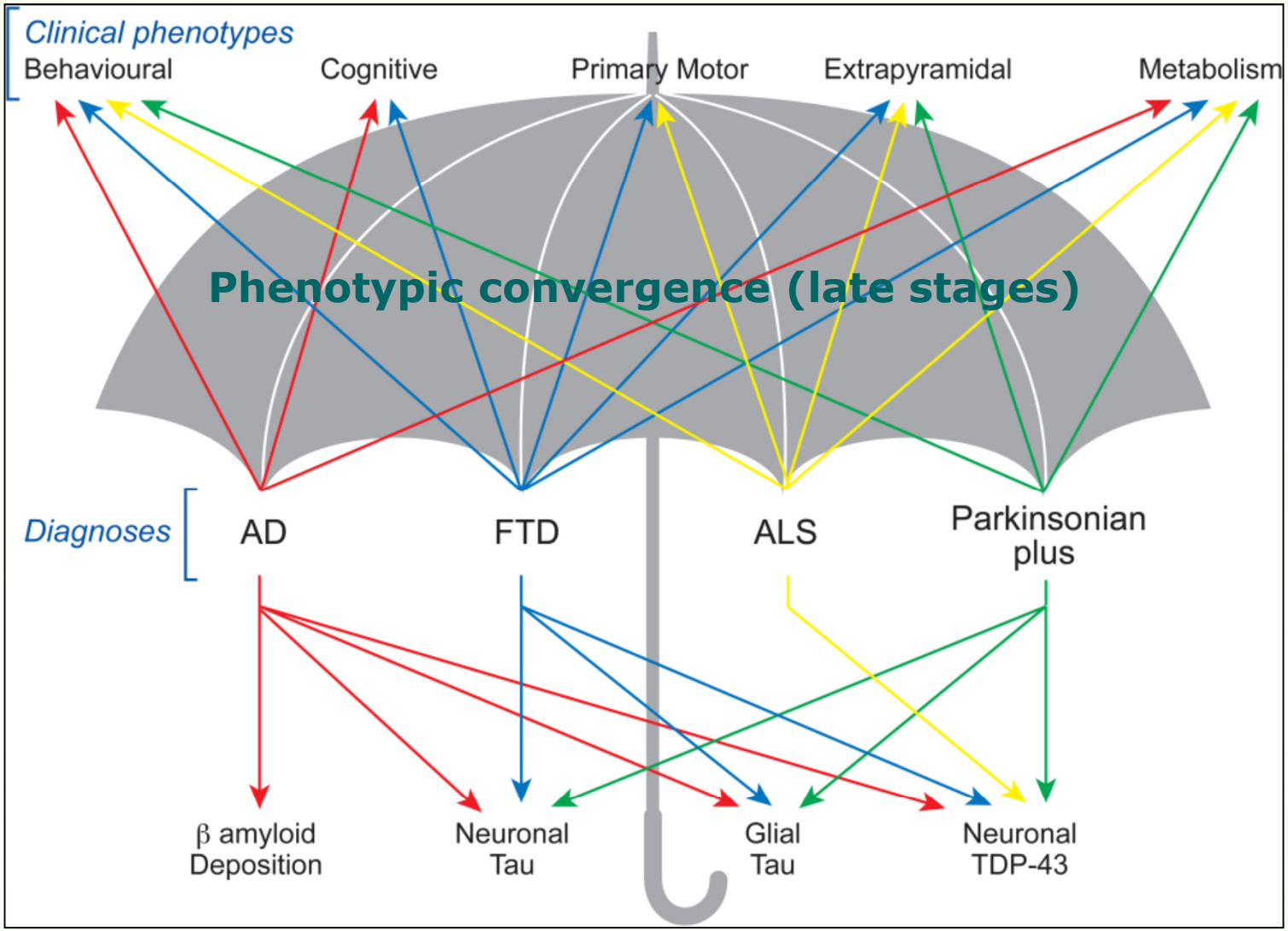
Molecular Nexopathies

Temporal evolution of disease and phenotypic heterogeneity



Molecular nexopathies: a new paradigm of neurodegenerative disease. Warren JD, Rohrer JD, Schott JM, Fox NC, Hardy J, Rossor MN. Trends Neurosci. 2013 Oct;36(10):561-9. doi: 10.1016/j.tins.2013.06.007.

Clinico-pathological presentation of NND

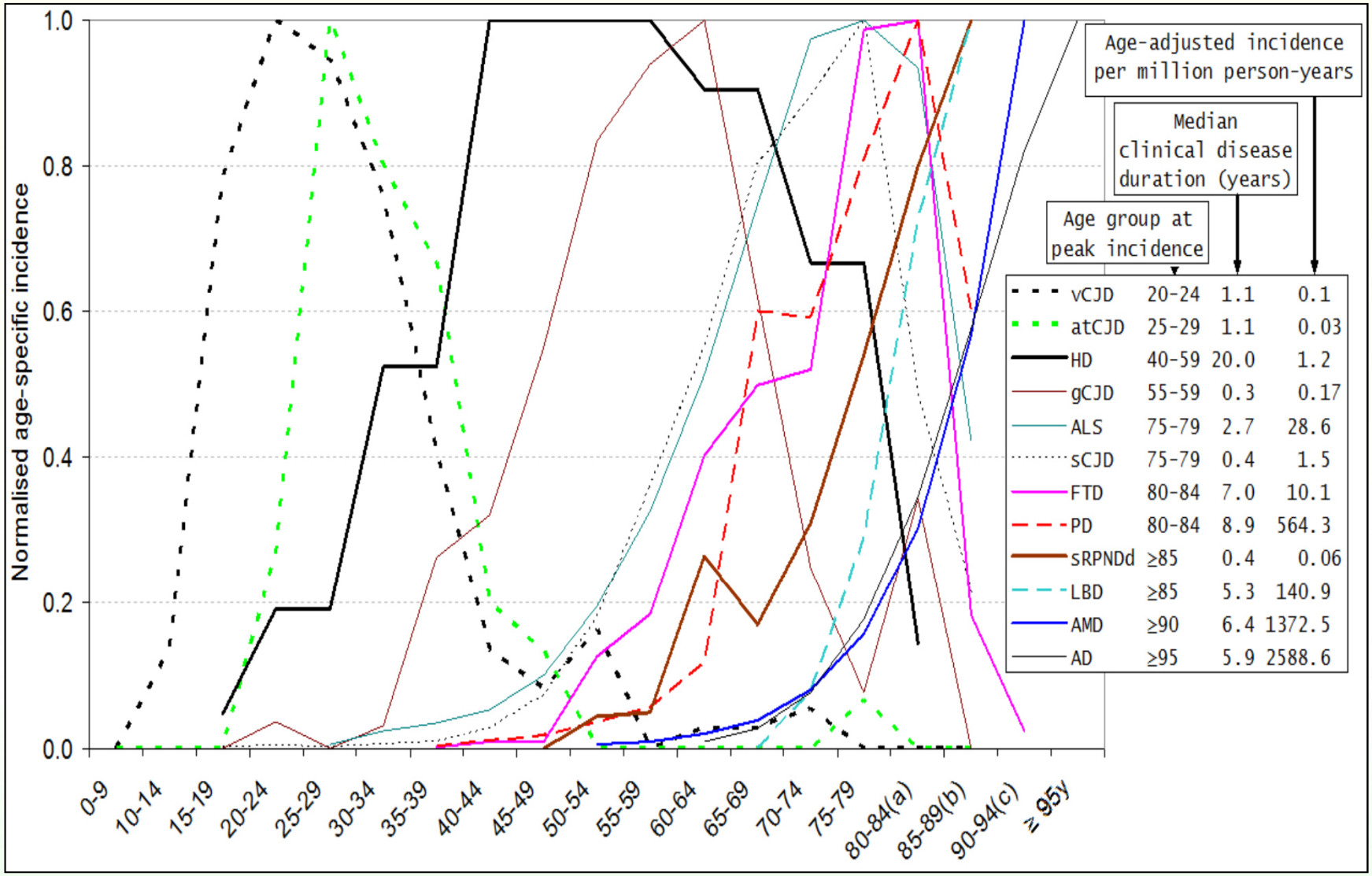


Clinical and pathological overlap in neurodegeneration: showing overlap at both a phenotypic and pathological level between multiple neurodegenerative conditions

Ahmed RM, et al. J Neurol Neurosurg Psychiatry 2016;0:1–8. doi:10.1136/jnnp-2014-308350

Epidemiology

1.- Diseases associated with aging, but …



Comparative Incidence of Conformational, Neurodegenerative Disorders. de Pedro-Cuesta J et al. (2015) PLoS ONE 10(9): e0137342. doi:10.1371/journal.pone.0137342

Outstanding Questions and Future Directions from a common approach to Neurodegeneration

1. Most Neurodegenerative Disorders can be considered to be proteinopathies ?
2. Common and Differential Approaches in NDD →
   - Diagnosis: Detection of the pathogenic agents
   - Treatment: Conversion and propagation (aggregation inhibitors, endocytic pathway, etc.).
3. Understanding the interaction with Comorbidities → as risk factors or drivers → Towars Precision Medicine
4. Seeding from out of the SNC, and Cross-seeding → Identification of new drivers/risk factors

CURRENT OPINION

Are comorbidities compatible with a molecular pathological classification of neurodegenerative diseases?

Curr Opin Neurol 2019, 32:000–000
DOI:10.1097/WCO.0000000000000664

Gabor G. Kovacs

Purpose of review
The purpose of this review is to provide an update on comorbidities in neurodegenerative conditions. The term comorbidity is used here to distinguish cases with overlapping pathogenic mechanisms, which includes combinations of neurodegenerative proteinopathies from cases with multimorbidity, which is defined as concomitant brain and systemic disorders with different pathogenic mechanisms.

Recent findings
Comorbid proteinopathies are more frequent in both sporadic and hereditary neurodegenerative diseases than previously assumed. The most frequent additional proteinopathies are related to Alzheimer's disease, Lewy body disorder, and limbic predominant transactive response DNA-binding protein 43 proteinopathy, however, different forms of tau pathologies are also increasingly recognized. In addition to ageing, synergistic interaction of proteins, common disease pathways, and the influence of genetic variations are discussed as possible pathogenic players.

Summary
Comorbid proteinopathies might influence the clinical course and have implications for biomarker and therapeutic development. As pure forms of proteinopathies are still observed, the notion of current molecular classification is justified. This corroborates elucidation of various pathogenic pathways leading to neurodegeneration. Assuming that single proteins and associated pathways are targeted in therapy trials, efforts are needed to better stratify patients and to select pure proteinopathy forms lacking unfavorable genetic constellations. Otherwise combined therapeutic strategies might be necessary for comorbid proteinopathies.

Keywords
classification, comorbidity, neurodegenerative diseases, proteinopathy

CURRENT OPINION

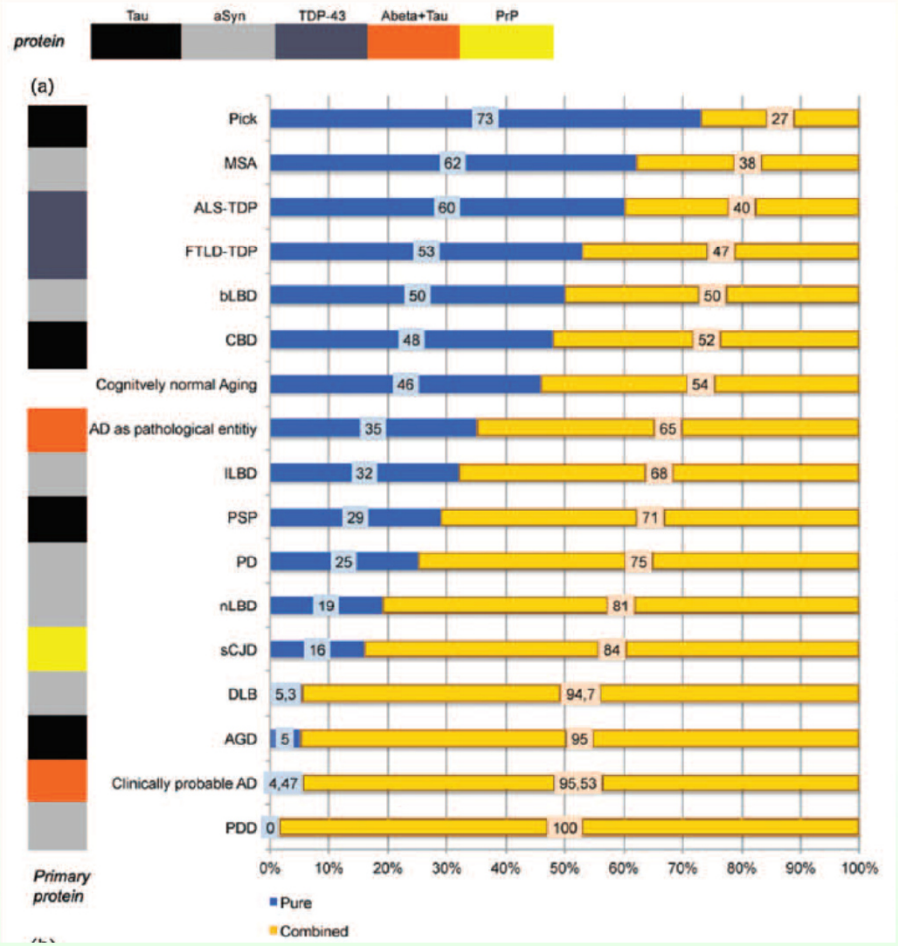
Are comorbidities compatible with a molecular pathological classification of neurodegenerative diseases?

Curr Opin Neurol 2019, 32:000–000
DOI:10.1097/WCO.0000000000000664

Gabor G. Kovacs

KEY POINTS

- Molecular classification of neurodegenerative diseases is protein-based.
- Recent molecular studies highlight that comorbid proteinopathies are more frequent than previously assumed.
- The most frequent additional proteinopathies are related to Alzheimer's disease, Lewy body disorder, and limbic predominant TDP-43 proteinopathy.
- The concept of comorbid proteinopathies has implications for biomarker and therapeutic development.
- Ageing, synergistic interaction of proteins, common disease pathways, and the influence of genetic variations are possible pathogenic players for comorbidity.
- Current molecular classification remains justified, but should be expanded to include comorbidities.



Human Type 2 Diabetes

Morphological Evidence for Abnormal β-Cell Function

Christine Sempoux, Yves Guiot, Dominique Dubois, Pierre Moulin, and Jacques Rahier

Diabetes 50 (Suppl. 1):S172–S177, 2001

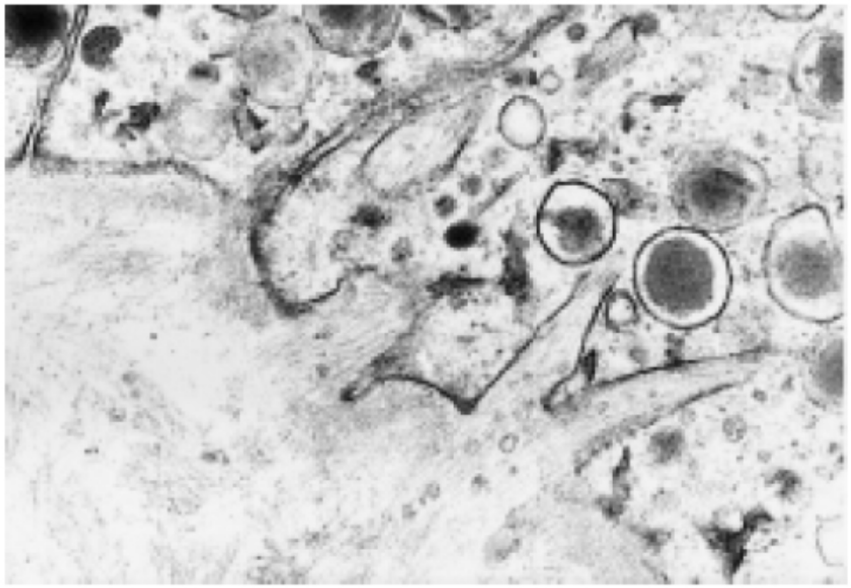


FIG. 2. Amyloid fibrils closely located at the β-cell membrane (electron microscopy, ×170,000).

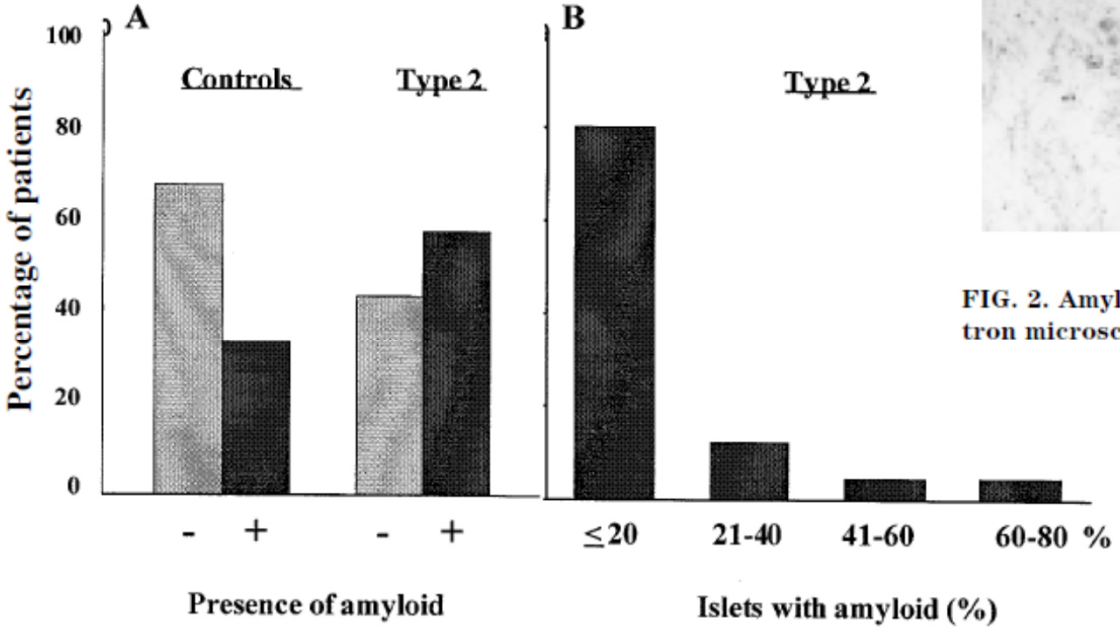


FIG. 3. *A*: Percentage of normoglycemic control subjects and type 2 diabetic patients with and without pancreatic amyloid deposit. *B*: Distribution of the relative percentage of amyloid-infiltrated islets in type 2 diabetic patients.

Physiol Rev 91: 795–826, 2011
doi:10.1152/physrev.00042.2009

ISLET AMYLOID POLYPEPTIDE, ISLET AMYLOID, AND DIABETES MELLITUS

Per Westermark, Arne Andersson, and Gunilla T. Westermark

Departments of Medical Cell Biology and Immunology, Genetics and Pathology, Uppsala University, Uppsala, Sweden

Westermark P, Andersson A, Westermark GT. Islet Amyloid Polypeptide, Islet Amyloid, and Diabetes Mellitus. *Physiol Rev* 91: 795–826, 2011; doi:10.1152/physrev.00042.2009.— Islet amyloid polypeptide (IAPP, or amylin) is one of the major secretory products of β-cells of the pancreatic islets of Langerhans. It is a regulatory peptide with putative function both locally in the islets, where it inhibits insulin and glucagon secretion, and at distant targets. It has binding sites in the brain, possibly contributing also to satiety regulation and inhibits gastric emptying. Effects on several other organs have also been described. IAPP was discovered through its ability to aggregate into pancreatic islet amyloid deposits, which are seen particularly in association with type 2 diabetes in humans and with diabetes in a few other mammalian species, especially monkeys and cats. Aggregated IAPP has cytotoxic properties and is believed to be of critical importance for the loss of β-cells in type 2 diabetes and also in pancreatic islets transplanted into individuals with type 1 diabetes. This review deals both with physiological aspects of IAPP and with the pathophysiological role of aggregated forms of IAPP, including mechanisms whereby human IAPP forms toxic aggregates and amyloid fibrils.

Physiol Rev 91: 795–826, 2011
doi:10.1152/physrev.00042.2009

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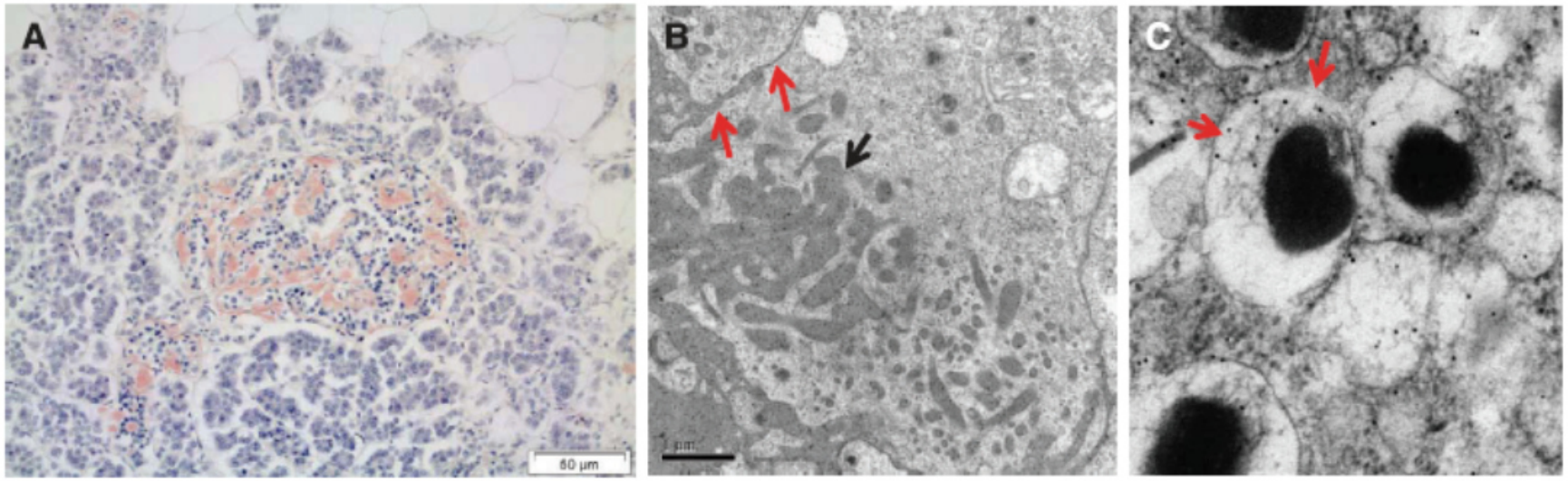


FIGURE 6 *A*: human pancreatic islet with extracellular amyloid deposits, a typical finding in type 2 diabetes. The section is stained for amyloid with Congo red. *B*: electron micrograph of a part of a β-cell with intracellular amyloid. Note the thin amyloid fibrils within the membrane-encircled compartments (black arrow). Amyloid between two cells is indicated by red arrows. *C*: electron micrograph of β-cell granules from human IAPP transgenic mouse fed a diet high in fat. Intragranular fibrils present in the halo region are immunolabeled with proIAPP specific antibodies (red arrows).

Physiol Rev 91: 795–826, 2011
doi:10.1152/physrev.00042.2009

ISLET AMYLOID POLYPEPTIDE, ISLET AMYLOID, AND DIABETES MELLITUS

Per Westermark, Arne Andersson, and Gunilla T. Westermark

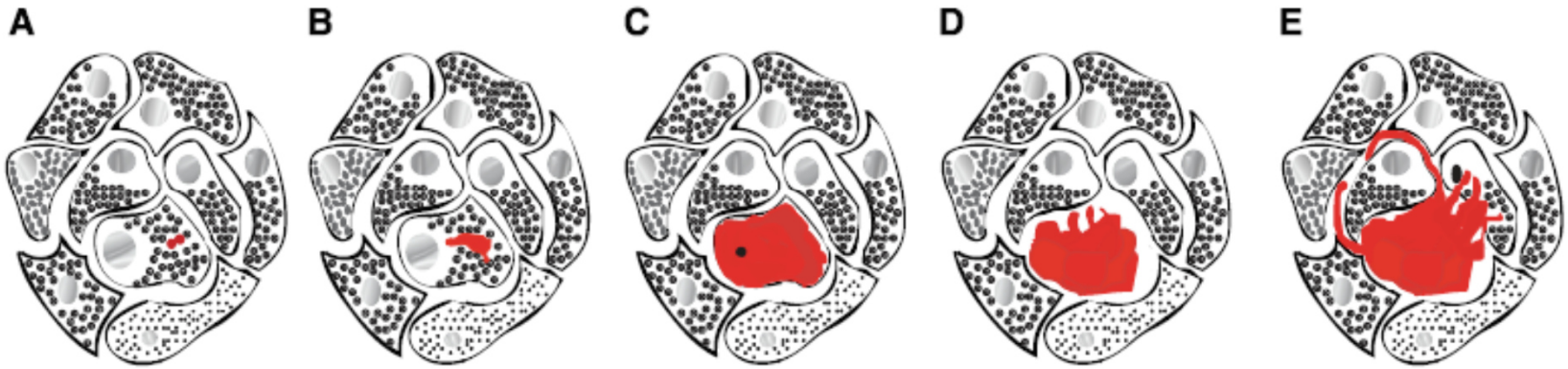
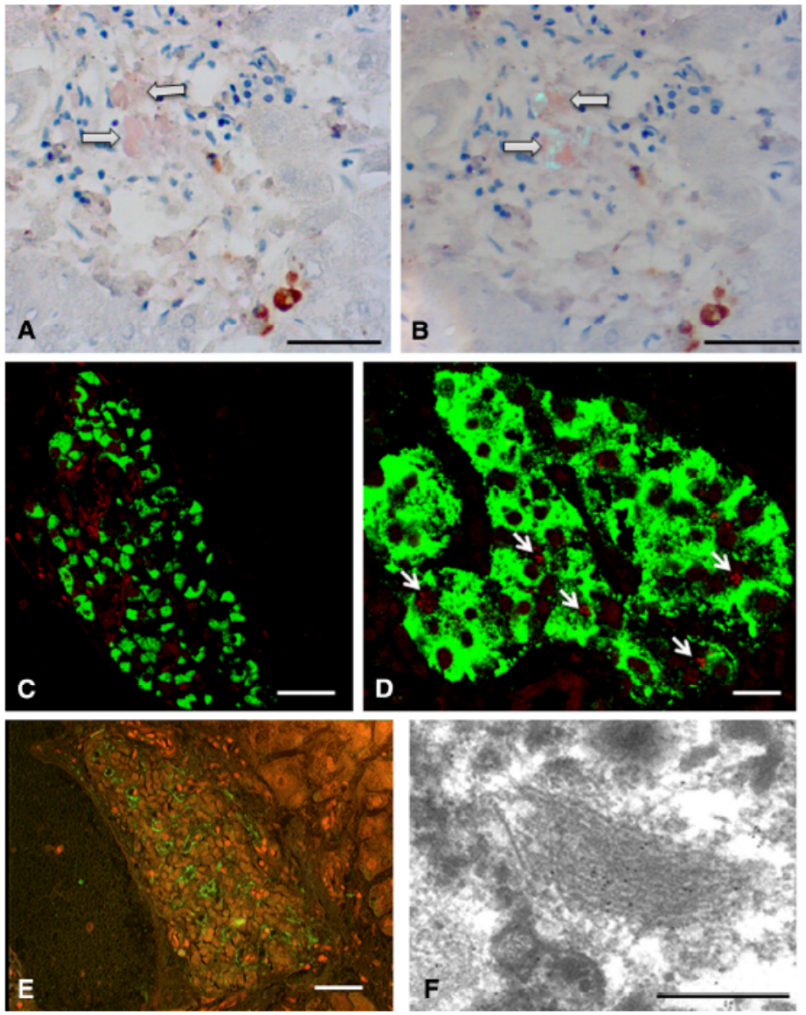


FIGURE 7 A hypothesis proposing how islet amyloid formation occurs. The initial amyloid accumulation occurs intracellularly and leads to extracellular deposits. *A*: the initial aggregation is intracellular and takes place in membrane-encircled compartments, e.g., secretory granules. At this location at least some of the amyloid is made up by proIAPP. *B*: deposited amyloid perforates membrane structures and fuses into larger deposits. *C*: in time the amyloid masses grow and replace the cytoplasmic compartment and induce apoptosis. *D*: amyloid that escapes degradation will remain extracellularly. *E*: at this location, the extracellular amyloid functions as a seed for propagation of deposits, which are now made up of mature IAPP, secreted from the surrounding β-cells. [Modified from Paulsson et al. (290), with kind permission from Springer Science + Business Media.]

Physiol Rev 91: 795–826, 2011
doi:10.1152/physrev.00042.2009

ISLET AMYLOID POLYPEPTIDE, ISLET AMYLOID, AND DIABETES MELLITUS

Per Westermark, Arne Andersson, and Gunilla T. Westermark

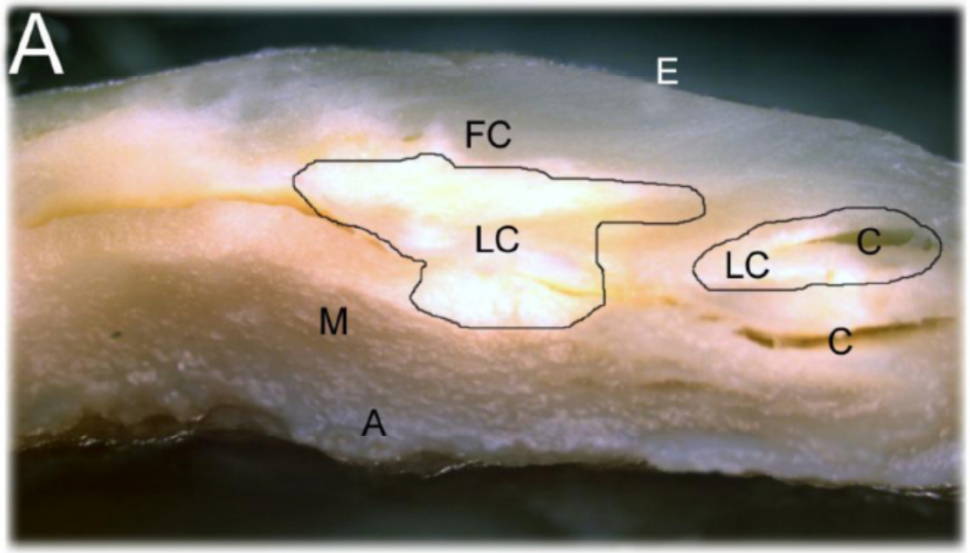


Amyloid deposits in transplanted islets in a patient with type 1 diabetes. A and B show an islet with heavy amyloid deposits, stained with Congo red and immunolabeled for insulin. Two insulin-containing cells are present after immunolabeling. The amyloid exhibits typical green birefringence in polarized light and is pointed out with white arrows. C and D display islets that are immunolabeled for glucagon (green) or C-peptide (green), respectively, and then labeled for amyloid with Congo red. Both islets show widely spread amyloid deposits. In E there is an islet with pronounced amyloid deposits, immunolabeled for IAPP (green). F is an electron micrograph showing a small intracellular amyloid deposit immunolabeled with antibodies against IAPP and visualized with gold

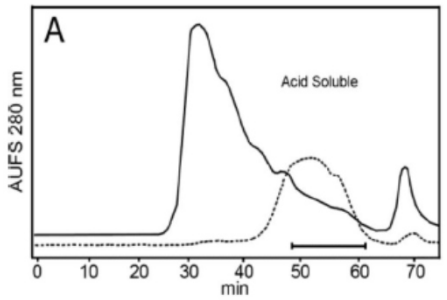
Published in final edited form as:
Biochim Biophys Acta. 2011 November ; 1812(11): 1508–1514. doi:10.1016/j.bbadis.2011.07.004.

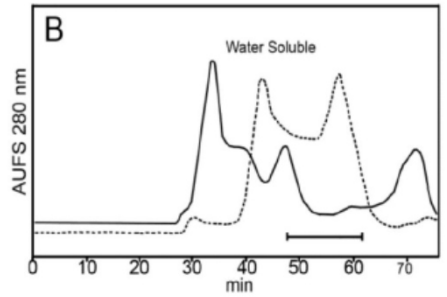
Chemical Characterization of Pro-inflammatory Amyloid-Beta Peptides in Human Atherosclerotic Lesions and Platelets

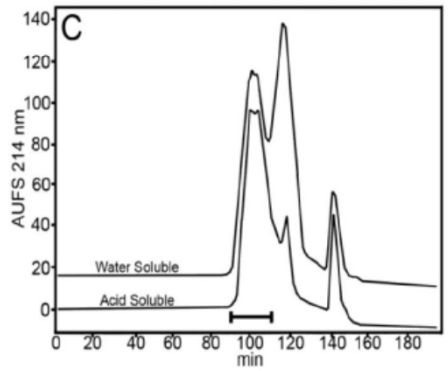
Tyler A. Kokjohn[a,b], **Gregory D. Van Vickle**[a,1], **Chera L. Maarouf**[a], **Walter M. Kalback**[a], **Jesse M. Hunter**[a], **Ian D. Daugs**[a], **Dean C. Luehrs**[a], **John Lopez**[c], **Daniel Brune**[c], **Lucia I. Sue**[d], **Thomas G. Beach**[d], **Eduardo M. Castaño**[e], and **Alex E. Roher**[a,*]

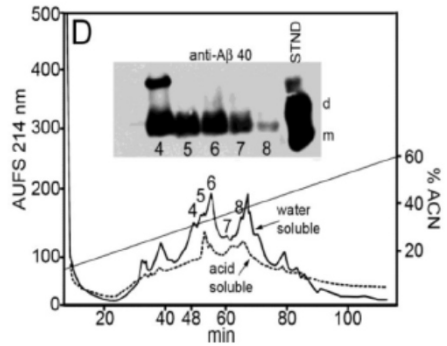


Representative human aorta atherosclerotic lesions. A) An example of the advanced aortic atherosclerotic lesions used in this study demonstrating lipid cores with areas of calcification underlying the fibrous cap. B) Complicated atherosclerotic lesions with ulceration and rupture of the fibrous caps showing areas of thrombosis. E = endothelium; FC = fibrous cap; LC = lipid cores; C = areas of calcification; M = tunica media; A = adventitia; T = thrombosis; UFC = ulcerated (crater-like) fibrous cap.









Untangling the role of amyloid in atherosclerosis

Geoffrey J. Howlett[a] and Kathryn J. Moore[b]

Curr Opin Lipidol 17:541–547.

Purpose of review

Amyloid deposits are a defining feature of several age-related and debilitating diseases. Their widespread presence in atherosclerotic plaques suggests a potential role in lesion development. This review discusses the proteins known to accumulate in atheroma and examines the evidence that amyloid-like structures activate macrophage signaling pathways linked to inflammation and prothrombotic potential.

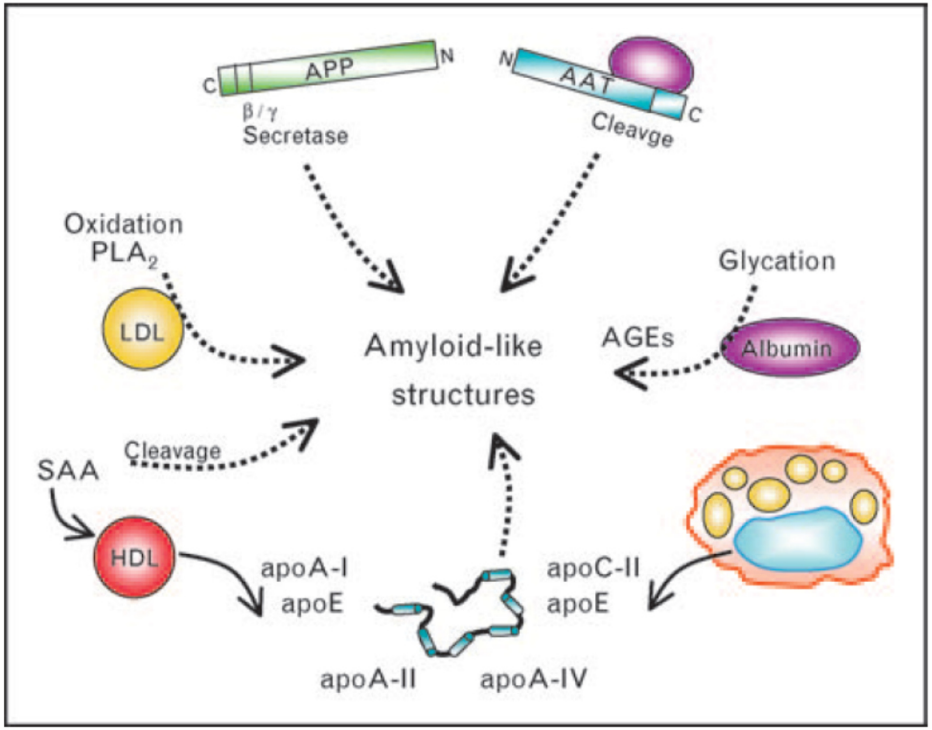
Recent findings

Numerous proteins that accumulate in atherosclerotic plaques form amyloid fibrils in vivo, including apolipoproteins, b-amyloid, and a1-antitrypsin. In addition, oxidation or enzymatic modification of low-density lipoproteins induces a structural reorganization of the particle, including the acquisition of amyloid-like properties.

Similarly, glycation of serum albumin, as observed in diabetes, is accompanied by the formation of aggregates with all the hallmarks of amyloid. Several receptors implicated in atherogenesis modulate the fate of amyloid fibrils by mediating their clearance (scavenger receptors A and B-I), activating inflammatory signaling cascades (receptor for advanced glycation endproducts), or both (CD36). Finally, recent studies indicate that amyloid deposition accelerates diet-induced atherosclerosis in mice.

Summary

Given the substantial evidence that amyloid fibrils or preamyloidogenic species are cytotoxic, the aberrant deposition of amyloid in the intima may be pathologically important in vascular inflammation and the promotion of atherosclerosis.



Amyloid-like structures may accumulate in atherosclerotic lesions as a result of lipoprotein modification, protein glycation, conformational constraints placed on lipid-poor apolipoproteins (apo's), and cleavage of amyloid precursor protein (APP), serum amyloid A (SAA), and α_1-antitrypsin. AA, amyloid A; PLA_2, phospholipase A_2; AGE, advanced glycation endproduct.

A brief elevation of serum amyloid A is sufficient to increase atherosclerosis[S]

J. Lipid Res. 2015. 56: 286–293.

Joel C. Thompson,*,† Colton Jayne,* Jennifer Thompson,* Patricia G. Wilson,* Meghan H. Yoder,* Nancy Webb,†,§ and Lisa R. Tannock[1,*,§,**]

Department of Internal Medicine, Division of Endocrinology and Molecular Medicine,* Department of Pharmacology and Nutritional Sciences, Division of Nutritional Sciences,† and Barnstable Brown Diabetes and Obesity Research Center,§ University of Kentucky, Lexington, KY; and Department of Veterans Affairs, Lexington, KY**

Serum amyloid A (SAA) has a number of proatherogenic effects including induction of vascular proteoglycans. Chronically elevated SAA was recently shown to increase atherosclerosis in mice. The purpose of this study was to determine whether a brief increase in SAA similarly increased atherosclerosis in a murine model. The recombination activating gene 1-deficient (rag1-/-) × apolipoprotein E-deficient (apoe -/-) and apoe -/- male mice were injected, multiple times or just once respectively, with an adenoviral vector encoding human SAA1 (ad-SAA); the injected mice and controls were maintained on chow for 12–16 weeks. Mice receiving multiple injections of ad-SAA, in which SAA elevation was sustained, had increased atherosclerosis compared with controls. Strikingly, mice receiving only a single injection of ad-SAA, in which SAA was only briefly elevated, also had increased atherosclerosis compared with controls. Using in vitro studies, we demonstrate that SAA treatment leads to increased LDL retention, and that prevention of transforming growth factor beta (TGF-b) signaling prevents SAA-induced increases in LDL retention and SAA-induced increases in vascular biglycan content. We propose that SAA increases atherosclerosis development via induction of TGF- b, increased vascular biglycan content, and increased LDL retention. These data suggest that even short-term inflammation with concomitant increase in SAA may increase the risk of developing CVD.

frontiers in Genetics

REVIEW
published: 06 October 2017
doi: 10.3389/fgene.2017.00126

Is Vascular Amyloidosis Intertwined with Arterial Aging, Hypertension and Atherosclerosis?

Yushi Wang, Xiaoxing Feng, Botao Shen, Jing Ma and Waiou Zhao**

TABLE 1 | The relationships among the four kinds of amyloid proteins, the arteries likely deposited, the cells likely involved and references.

Amyloid protein	Arterial tree	Cellular role
TTR	Coronary Booth et al., 1995, Cerebral Sekijima, 2015	EC Nunes et al., 2013
Apo1	Coronary Stewart et al., 2007, Aorta Mucchiano et al., 2001	Matrix Ramella et al., 2011
Immunoglobin γ	Cerebra Audemard et al., 2012	EC Truran et al., 2014, Matrix Berghoff et al., 2003
Medin	Aorta Davies et al., 2015a, Cerebral Peng et al., 2005	EC Davies et al., 2015b, VSMC Hagggvist et al., 1999

JAMA | Original Investigation

Association Between Midlife Vascular Risk Factors and Estimated Brain Amyloid Deposition

Rebecca F. Gottesman, MD, PhD; Andrea L. C. Schneider, MD, PhD; Yun Zhou, PhD; Josef Coresh, MD, PhD; Edward Green, MD; Naresh Gupta, MD; David S. Knopman, MD; Akiva Mintz, MD; Arman Rahmim, PhD; A. Richey Sharrett, MD, DrPH; Lynne E. Wagenknecht, DrPH; Dean F. Wong, MD, PhD; Thomas H. Mosley, PhD

Key Points

Question Are midlife vascular risk factors associated with late-life brain amyloid deposition?

Findings In a prospective cohort study of 346 members of the community-based Atherosclerosis Risk in Communities (ARIC)–PET cohort without dementia, having 2 or more midlife vascular risk factors compared with none was significantly associated with elevated amyloid deposition in the brain (61.2% vs 30.8%). There was no significant association for late-life risk factors.

Meaning These findings are consistent with a role of vascular disease in the development of Alzheimer disease.

Molecular and cellular basis of NDD

1. Conformational Disorders (protein misfolding disorders) → Dual Etiology
2. Gain of function vs. Loss of function
3. Molecular Transmisibility
4. Cellular susceptibility and prion like transmission → Clinical presentation and Disease progression
5. Aggregates vs. Diffusible toxic molecules → Partial correlation between lesions and neurodegeneration
6. Nexopathies → phenotypic convergence
7. Drivers → Risk factors & co-existence of NDD