Prions

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From Microbes to Prions: The Final Proof of the Prion Hypothesis

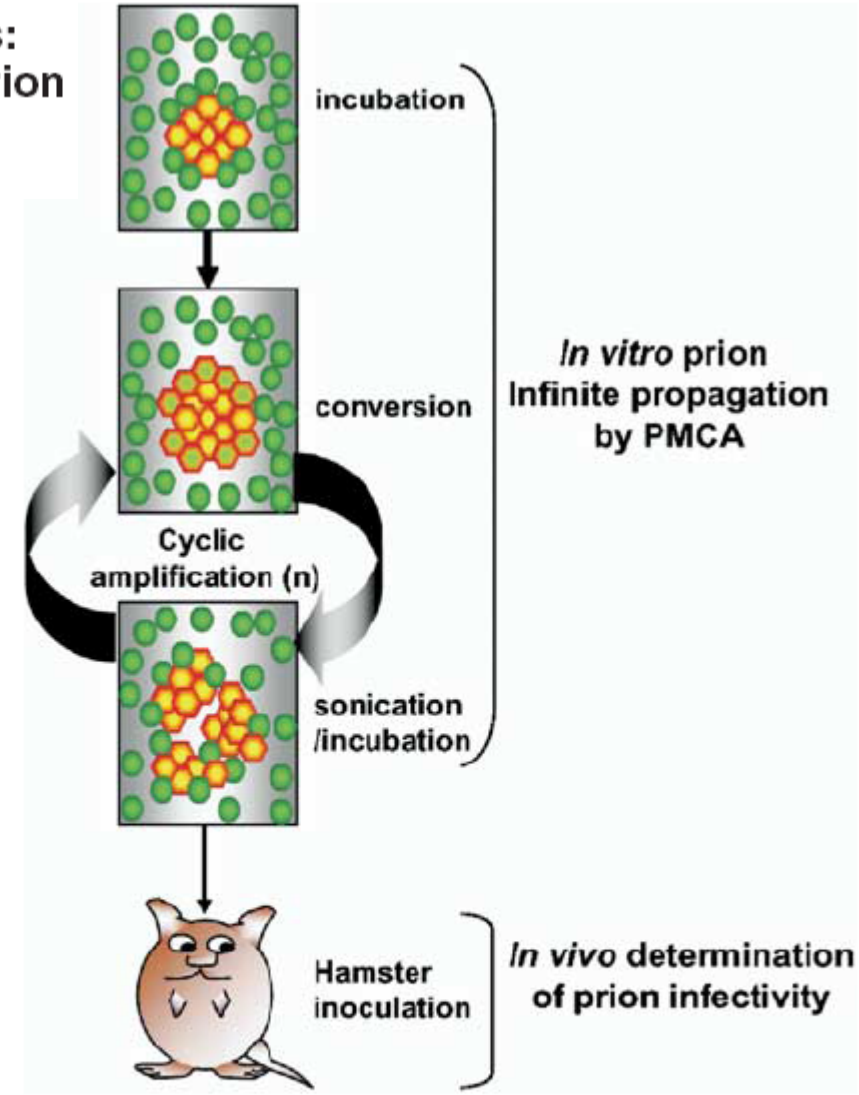


Figure 2. Prion Propagation In Vitro by PMCA and Detection of the Infectivity of the In Vitro-Generated Prions by Inoculation to Hamster

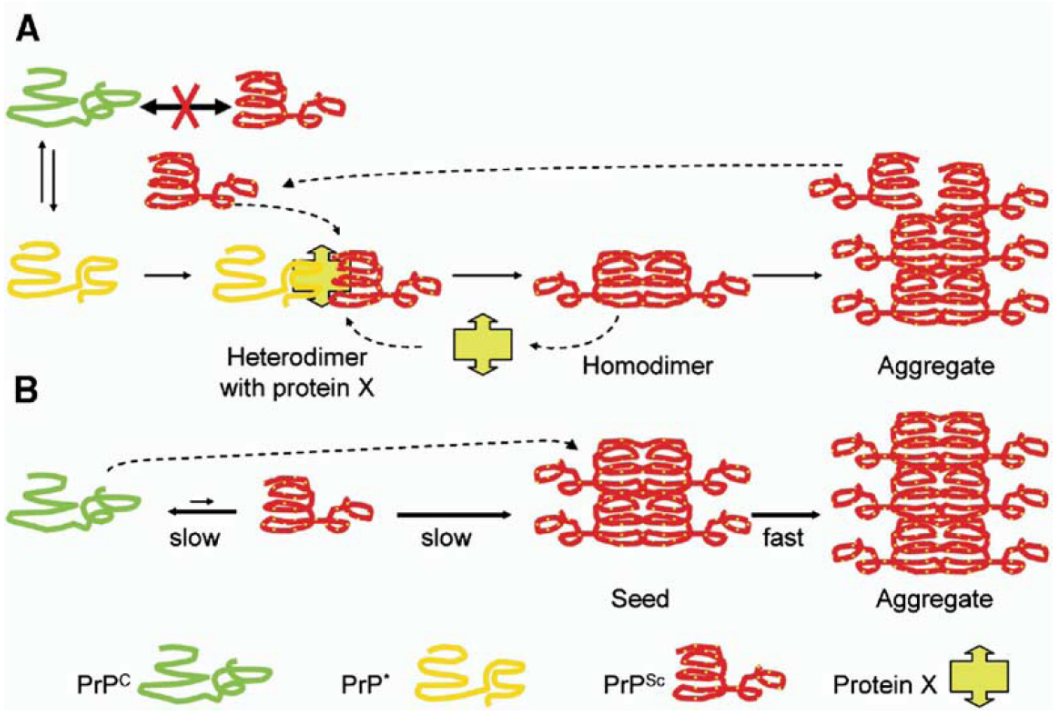
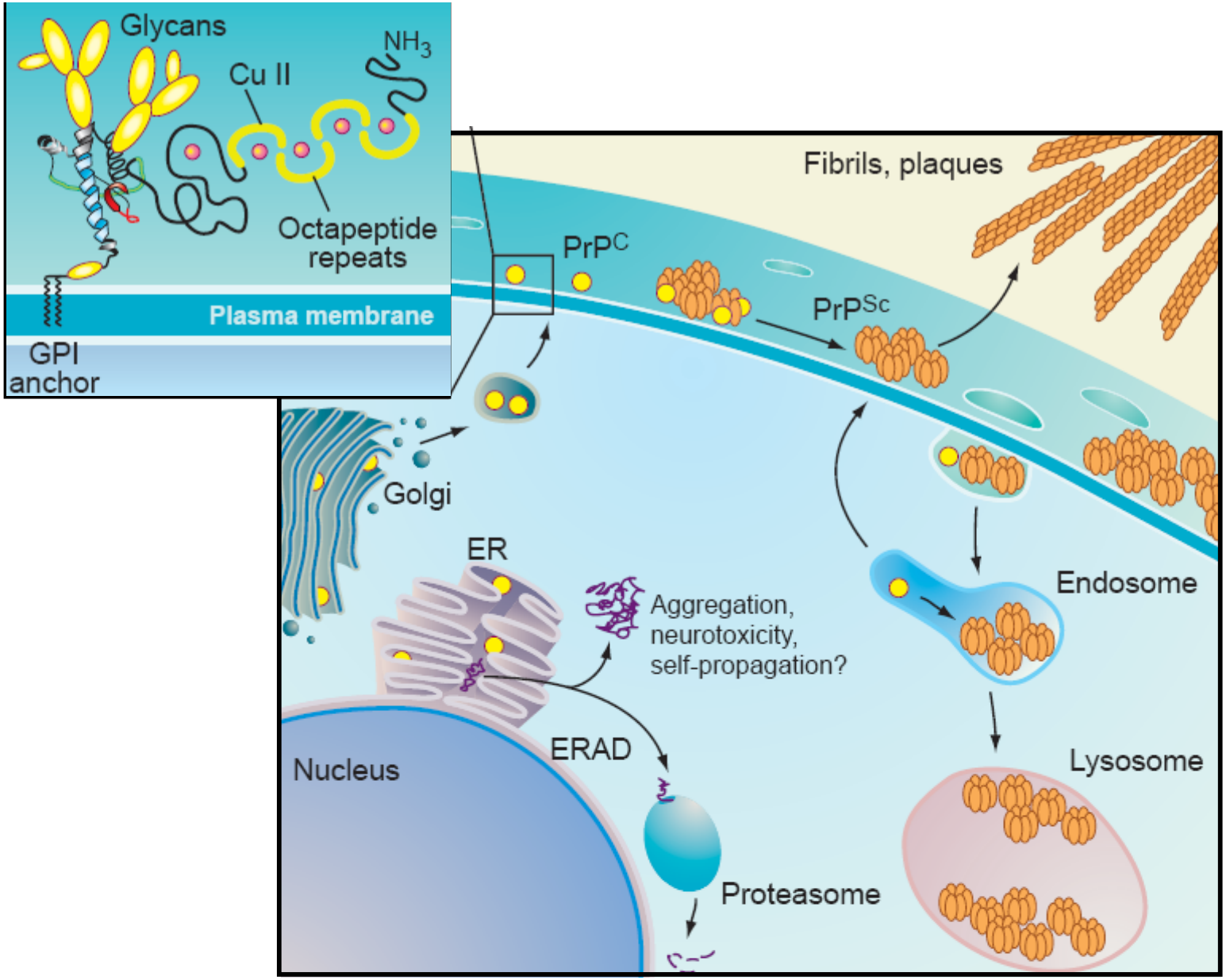


Figure 1. Refolding and Seeding Models of PrP^{C} to PrP^{Sc} Conversion

(A) The "refolding" model contends that a high energy barrier prevents spontaneous conversion of PrP^{C} (green) to PrP^{Sc} (red), but PrP^{C} is in equilibrium with the conformationally intermediate form PrP* (orange). PrP* can bind to PrP^{Sc} via a currently uncharacterized factor referred to as protein X (yellow box). This heterodimer reverts to PrP homodimer and forms large aggregates. Protein X is recycled while PrP^{Sc} monomers or oligomers break off from the PrP^{Sc} aggregates and form new heterodimers maintaining the autocatalytic process.

(B) According to the "seeding" model, PrP^{C} and PrP^{Sc} are in reversible thermodynamic equilibrium. When several monomeric PrP^{Sc} molecules form a highly ordered nucleus, PrP^{C} can be rapidly recruited into the PrP^{Sc} nucleus.


Glycans
NH3
Cu II
Octapeptide repeats
Plasma membrane
GPI anchor
Fibrils, plaques
PrPC
PrPSc
Golgi
ER
Aggregation, neurotoxicity, self-propagation?
Endosome
Nucleus
ERAD
Lysosome
Proteasome

Cellular trafficking of PrP^C and PrP^{Sc}. PrP^C (yellow dots) follows the secretory pathway of the cell through the endoplasmic reticulum (ER) and the Golgi. Mature PrP^C is inserted via its GPI anchor into plasma membrane lipid rafts. The conversion of PrP^C to PrP^{Sc} (orange ovals) occurs either on the cell surface or, following endocytosis, in a cellular compartment such as the endosome. PrP^{Sc} formed at the surface and released into the extracellular space may cause the plaques seen in TSE diseases such as human vCJD. The diffuse PrP^{Sc} deposits and neuronal vacuolation common to many sheep scrapie strains may be due to PrP^{Sc} formation in endocytic compartments or to endocytosed surface PrP^{Sc} accumulating inside the cell. Misfolded PrP^C (squiggle) accumulating in the cytosol may also trigger PrP^{Sc} formation. (**Inset**) Structure of PrP^C showing the GPI anchor, the glycan chains, the copper-binding octapeptide repeats, and the regions where the α helices and loop structure of PrP^C (red, blue) may be converted to the β sheets of PrP^{Sc}. ERAD, endoplasmic reticulum associated degradation.