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BULLETIN N° 234
ACADÉMIE EUROPEENNE INTERDISCIPLINAIRE DES SCIENCES
INTERDISCIPLINARY EUROPEAN ACADEMY OF SCIENCES

Lundi 1er avril 2019 :
à 16h
à l'Institut Henri Poincaré salle 421
11, rue Pierre et Marie Curie 75005 PARIS/Métro : RER Luxembourg

Conférence :

" Progrès récents dans le transport de molécules au travers des membranes cellulaires, ou comment des molécules polaires de haut poids moléculaire peuvent traverser une barrière imperméable sans systèmes de transport spécialisés."

par Sandrine SAGAN, Directrice de Recherche CNRS,
Laboratoire des Biomolécules (UMR 7203 CNRS-ENS-SU), Paris

Notre Prochaine séance aura lieu le lundi 6 mai 2019 à 16h
à l'Institut Henri Poincaré salle 314

Elle aura pour thème

Conférence:

" Biologie quantitative de la communication entre neurones: instabilité moléculaire et mémoire, du normal au pathologique"

par Antoine TRILLER,
membre de l'Académie des Sciences
Directeur de Recherche (CE) INSERM,
Institut de Biologie de l'École Normale Supérieure
(ENS . CNRS UMR8197 . Inserm U1024)

ACADÉMIE EUROPÉENNE INTERDISCIPLINAIRE DES SCIENCES
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Avril 2019

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TABLE DES MATIERES

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Conférence:

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ACADEMIE EUROPEENNE INTERDISCIPLINAIRE DES SCIENCES

Fondation de la Maison des Sciences de l'Homme, Paris.

Séance du Lundi 1er avril 2019/IHP 16h

La séance est ouverte à 16h **sous la Présidence de Victor MASTRANGELO** et en la présence de nos Collègues Gilbert BELAUBRE, Jean BERBINAU, Jean-Louis BOBIN, Eric CHENIN, Gilles COHEN-TANNOUDJI, Sylvie DERENNE, Claude ELBAZ, Michel GONDRAN, Irène HERPE-LITWIN, Claude MAURY, Marie-Françoise PASSINI, Edith PERRIER, Jean SCHMETS, Alain STAHL, Jean-Paul TEYSSANDIER, Jean-Pierre TREUIL .

Etaient excusés :François BEGON, Jean-Pierre BESSIS, Bruno BLONDEL, Michel CABANAC, Alain CARDON, Juan-Carlos CHACHQUES, Alain CORDIER , Daniel COURGEAU, Ernesto DI MAURO, Jean-Felix DURASTANTI, Françoise DUTHEIL, Vincent FLEURY, Robert FRANCK, Jean -Pierre FRANCOISE, Jacques HENRI-ROBERT, Dominique LAMBERT, Pierre MARCHAIS, Anastassios METAXAS, Jacques NIO, Pierre PESQUIES, Jacques PRINTZ, Denise PUMAIN, René PUMAIN, Michel SPIRO, Mohand TAZEROUT, Jean VERDETTI.

Etait présent notre collègue membre correspondant Benoît PRIEUR

I. Conférence de Sandrine SAGAN

A. **Présentation du conférencier par notre Président Victor MASTRANGELO**.

Notre conférencière nous a communiqué une esquisse de sa carrière:

Dr Sandrine SAGAN, Directrice du Laboratoire des Biomolécules,
UMR 7203 CNRS - ENS - SU, Département de Chimie,
équipe « Biomolécules : Analyse, Interactions Moléculaires et Cellulaires »

Mots clés de Recherche*: Biochimie, chimie, pharmacologie, peptides, peptides à pénétration cellulaire, Interactions peptide/membrane, protéines membranaires, récepteur couplé à la protéine-G (GPCR), photolabeling, spectrometrie de masse MALDI-TOF, calorimétrie IT et DS, spectroscopie et microscopie de fluorescence.*

Esquisse biographique:
Sandrine Sagan a fait des études de 1er et second cycle de biochimie et Pharmacologie à l'Université Pierre et Marie Curie (UPMC) à Paris. Elle a obtenu en 1991 un Doctorat de Pharmacologie Moléculaire et Cellulaire portant sur les relations structure-activité des peptides opioïdes à l'Insitut Jacques Monod. Pendant cette période, elle a également travaillé quelques mois dans le groupe de Hans W. Kosterlitz (Aberdeen, Écosse), qui a identifié les premières enképhalines peptides opioïdes. Après un post-doctorat à l'Institut de Biologie Moleculaire (Salzbourg, Autriche), elle a rejoint en tant que chercheuse le département de Chimie du CNRS à l'UPMC en 1993, et elle a travaillé dix-huit mois dans le groupe de Jacques Glowinski (INSERM U 114, Collège-de-France). Son projet était axé sur le récepteur de membrane tachykinin NK-1 en utilisant la spectrométrie de masse/photolabelling et les approches pharmacologiques pour comprendre les bases moléculaires pour l'interaction de la Substance P à ligand de peptide naturel avec le récepteur. Ses domaines d'intérêt de recherche actuels sont dédiés aux aspects fondamentaux de la membrane cellulaire: mécanismes de pénétration cellulaire et/ou activité lytique (antimicrobienne) des

peptides/protéines pendant leur interaction avec les membranes cellulaires.

Education
• PhD (Paris 6), Pharmacologie Moléculaire et Cellulaire, 1991
• « Habilitation à diriger des Recherches », UPMC (Paris 6), 1997.

Fonctions académiques
2014- Directeur du Laboratoire des Biomolécules, UMR7203 CNRS –UPMC - ENS
2015 DR1 CNRS (section 16 INC)
2012-2016 Nomination en tant que membre, de la section 16 CoNRS, Chimie des organismes vivants et Chimie médicinale. Design et propriétés de composés d' intérêt biologique.
01/2011- Membre du conseil scientifique du LABEX (Laboratory of excellence) MiChem
2009-2016 Chef d'Équipe « Biomolecules : Analyse, Interactions Moléculaire et Cellulaire »
2007-08 Directeur adjoint de l' Unité de Recherche UMR 7613
2005 DR2 CNRS UMR 7613 UPMC-CNRS dirigée par la Professeure Solange Lavielle.
1997-2005 CR1, UMR CNRS 7613 dirigée par Prof. A. Marquet, puis par S. Lavielle (Mai 1999).
1993-1997 CR2, URA CNRS 493, dirigée par Prof. M. Gaudry, puis Andrée Marquet.
1992-1993 Bourse post-doctorale du Ministère de la Recherche MRE
1989-1992 Allocataire de recherche – Monitrice de l'Enseignement Supérieur

Récompenses
Coordinatrice de projets subventionnés (PRC-JSPS-CNRS, ERA-NET, ANR, ANRS, Fondation ARC, PHC-Balaton)
Lauréate de la médaille de bronze du CNRS (département de Chimie) en 2001
CDTM « Advanced Drug Delivery Reviews » Prize, Cardiff, 2008
Bourse post-doctorale du ministère français des relations extérieures of (MRE)
Bourse Embo 1990 au Royaume Uni

Expérience de Recherche
2009- Laboratoire des Biomolécules, Paris, France
1995-2008 Laboratoire de Synthèse, Structure et Fonction des molécules bioactives, Paris, France
1993-1995 Chaire de Neuropharmacologie (J Glowinski), Collège-de-France, Paris, France
1992-1993 Institut de Biologie Moléculaire Bourse post-doctorale MRE (G. Kreil), Salzbourg, Autriche
1989-1990 Unité de Recherche sur les traitements addictives (H. Kosterlitz), EMBO fellow, Marischal College, Aberdeen, Scotland.
1989-1991 : Laboratoire de Bioactivation des Peptides (P. Nicolas), Institut J. Monod, Paris, France

Production scientifique:
(https://orcid.org/0000-0003-0083-4411)
95 publications and 12 actes de colloque (4000 citations Google Scholar), 64 invitations à des conférences et séminaires,
5 chapitres de livres, > 150 communications orales et de poster

II. Conférence

Résumé de la conférence:

" Progrès récents dans le transport de molécules au travers des membranes cellulaires, ou comment des molécules polaires de haut poids moléculaire peuvent traverser une barrière imperméable sans systèmes de transport spécialisés."

Les membranes sont présentes à tous les niveaux d'organisation des organismes vivants. Longtemps présentée comme une barrière passive séparant la cellule de son environnement, la membrane plasmique joue un rôle majeur dans l'homéostasie cellulaire en assurant des fonctions dynamiques cruciales de contrôle et de traitement de l'information en réponse aux nombreux stimuli extérieurs. Malgré sa composition moléculaire simple (lipides, protéines, glucides), son organisation spatio-temporelle complexe confère à la membrane plasmique des propriétés de déformation, courbure et d'élasticité très dynamiques. Des systèmes protéiques de transport actif sophistiqués contrôlent les échanges à travers la membrane pour importer des nutriments essentiels. Depuis une trentaine d'années, il est connu que des nanoobjets de taille importante et polaires comme des peptides ou des protéines sont capables de traverser la membrane plasmique sans utiliser ses systèmes de transport actifs. J'illustrerai à l'aide d'exemples récents les aspects physico-chimiques qui permettent d'appréhender et dévoiler ces nouveaux mécanismes de passage des membranes.

Un compte-rendu détaillé, voire **un enregistrement audio-vidéo** agréé par le conférencier, sera prochainement disponible sur le site de l'AEIS http://www.science-inter.com.

REMERCIEMENTS

Nous tenons à remercier vivement Mme Sylvie BENZONI Directrice de l'Institut Henri POINCARÉ et Mmes Florence LAJOINIE et Chantal AMOROSO ainsi que les personnels de l'IHP pour la qualité de leur accueil.

Documents

- Pour préparer la conférence d'Antoine TRILLER , nous vous proposons :

  p. 07 : un résumé de sa conférence *" Biologie quantitative de la communication entre neurones: instabilité moléculaire et mémoire, du normal au pathologique"*

  p. 08 : paru sur le site https://www.ibens.ens.fr/spip.php?rubrique22 une brève présentation par Antoine TRILLER de la biologie cellulaire de la synapse en relation avec sa conférence

  p. 09: un article d'Antoine TRILLER et al. intitulé "*Physico-Pathologic Mechanisms Involved in Neurodegeneration: Misfolded Protein-Plasma Membrane Interactions*" paru dans Neuron 95, July 5, 2017

Résumé Article Antoine TRILLER:

Biologie quantitative de la communication entre neurones:
instabilité moléculaire et mémoire, du normal au pathologique.

Les neurones communiquent entre eux et forment des réseaux qui sont à l'origine des propriétés du système nerveux. Cette communication se fait au niveau de jonctions appelées "synapse". Les composants moléculaires des synapses sont instables et bougent tout le temps par des processus de diffusion. Ceci est à l'origine d'un paradoxe que nous aborderons: comment assurer une mémoire stable quand toutes les molécules bougent. Nous évoquerons ensuite les conséquences des altérations de ces mouvements dans des pathologies neurodégénératives comme la maladie d'Alzheimer ou de Parkinson.

Biologie cellulaire de la synapse

https://www.ibens.ens.fr/spip.php?rubrique22

par Antoine TRILLER Institut de Biologie de l'École Normale Supérieure ENS . CNRS UMR8197 . Inserm U1024

Contexte

Les neurones détectent, intègrent et transmettent l'information de manière efficace grâce à la spécialisation de leur membrane en sous domaines fonctionnels et structuraux comme la zone active ou la membrane post synaptique. L'efficacité et la précision de la neurotransmission dépendent fortement de deux propriétés apparemment antagonistes de la membrane synaptique : la stabilité de son organisation, et sa capacité de s'adapter rapidement aux modifications environnementales.

De plus, la stabilité structurale des synapses doit être assurée malgré la fluidité des membranes. En effet, les molécules des membranes bougent en effet dans le plan de la membrane du fait de l'agitation thermique brownienne, qui tend à favoriser leur distribution homogène. Les neurones dépensent donc de l'énergie pour contrôler ces mouvements et maintenir les molécules à des sites particuliers par des mécanismes qui diminuent cette fluidité. **Notre équipe s'intéresse à la régulation de la dynamique des récepteurs synaptiques par les différents éléments (structuraux ou fonctionnels) qui constituent la synapse**.

Résultats marquants

Ces dix dernières années, l'équipe a abordé ces paradoxes conceptuels en développant de nouveaux outils technologiques et analytiques pour suivre le comportement des composants synaptiques au niveau de la molécule unique et ainsi changer l'échelle d'analyse. Plus précisément, les chercheurs ont développé le suivi et l'analyse de particule unique par des nanocristaux (quantum-dots). Nous avons montré qu'il existe des échanges rapides de récepteurs entre les sites synaptiques et extra synaptiques et a établi que la stabilisation transitoire des récepteurs aux synapses se fait par des interactions avec des protéines partenaires comme les protéines d'échafaudage. Les techniques d'imagerie en super-résolution (PALM, STORM) ont permis l'accès à l'organisation détaillée de ces structures post-synaptiques. Les régulations des interactions récepteurs-échafaudage et intra-échafaudage apparaissent comme un principe central de la régulation du nombre de récepteurs aux synapses.

Fossati M, Pizzarelli R, Schmidt ER, Kupferman JV, Stroebel D, Polleux F, Charrier C (2016) SRGAP2 and Its Human-Specific Paralog Co-Regulate the Development of Excitatory and Inhibitory Synapses. Neuron 91:356-69

Cantaut-Belarif Y, Antri M, Pizzarelli R, Colasse S, Vaccari I, Soares S, Renner M, Dallel R, Triller A*, Bessis B* (2017) Microglia control the glycinergic but not the GABAergic synapses via prostaglandin E2 in the spinal cord J Cell Biol 216:2979-2989

Shrivastava AN, Aperia A, Melki R, Triller A (2017) Physico-Pathologic Mechanisms involved in Neurodegeneration : Misfolded Proteins-Plasma Membrane Interactions. Neuron 95(1):33-50 ; doi : 10.1016

Shrivastava AN, Redeker V, Fritz N, Pieri L, Almeida LG, Spolidoro M, Liebmann T, Bousset L, Renner M, Léna C, Aperia A, Melki R, Triller A (2015) α-synuclein assemblies sequester neuronal a3-Na+/K+-ATPase and impair Na+ gradient. EMBO J 34:2408-23

Specht CG, Izeddin I, Rodriguez PC, El Beheiry M, Rostaing P, Darzacq X, Dahan M, Triller A (2013) Quantitative nanoscopy of inhibitory synapses : counting gephyrin molecules and receptor binding sites. Neuron 79:308-321

Neuron
Review

Physico-Pathologic Mechanisms Involved in Neurodegeneration: Misfolded Protein-Plasma Membrane Interactions

Amulya Nidhi Shrivastava,[1,2] Anita Aperia,[3,*] Ronald Melki,[2,*] and Antoine Triller[1,*]
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http://dx.doi.org/10.1016/j.neuron.2017.05.026

Several neurodegenerative disorders, such as Alzheimer's and Parkinson's disease, are characterized by prominent loss of synapses and neurons associated with the presence of abnormally structured or misfolded protein assemblies. Cell-to-cell transfer of misfolded proteins has been proposed for the intra-cerebral propagation of these diseases. When released, misfolded proteins diffuse in the 3D extracellular space before binding to the plasma membrane of neighboring cells, where they diffuse on a 2D plane. This reduction in diffusion dimension and the cell surface molecular crowding promote deleterious interactions with native membrane proteins, favoring clustering and further aggregation of misfolded protein assemblies. These processes open up new avenues for therapeutics development targeting the initial interactions of deleterious proteins with the plasma membrane or the subsequent pathological signaling.

Misfolding and aggregation of amyloid-β (Aβ), tau, α-synuclein (α-syn), superoxide dismutase 1 (SOD1), and huntingtin exon 1 (HTTexon1) are tightly linked to Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and Huntington's disease (HD), respectively (Goedert et al., 2010; Goedert, 2015). The ability of these protein particles to transfer from one cell to another, similar to the aggregated form of the prion protein (PrP^{RES}; RES, resistant to proteolysis) in Creutzfeldt-Jakob disease (CJD), accounts for the widespread pathophysiology seen in neurodegenerative disorders. The cell-to-cell "prion-like" transfer of misfolded protein aggregates involves release from one neuron, uptake by nearby neurons, and, last, seeded assembly of misfolded host proteins in recipient neurons. Several excellent reviews cover the topic of cell-to-cell transfer in detail (Brundin et al., 2010; Jucker and Walker, 2013); however, the pathophysiological effect of misfolded protein aggregates binding to the plasma membrane, including interaction with the biomolecules therein, in particular under non-acute experimental conditions, has not been specifically addressed. In this review, we discuss biophysical mechanisms that regulate the behavior of pathogenic assemblies following release from the donor neuron prior to their internalization within the recipient neurons. The review will focus on experimental evidence showing that pathogenic proteins bind to several biomolecules (proteins, lipids, and carbohydrates) at the plane of the plasma membrane. These stochastic interactions initiate multiple deleterious signaling pathways that can directly or indirectly trigger a cascade of events that ultimately lead to pathological symptoms. They also play a key role in pathogenic protein uptake, seeded aggregation of the endogenous proteins, and rapid proteostasis collapse. Thus, the interactions of pathogenic assemblies with membrane components very likely contribute to and add on cell autonomous factors that increase the vulnerability of healthy neurons (Saxena and Caroni, 2011; Surmeier et al., 2017).

Structure of Pathogenic Protein Assemblies and Pathology

The constituents of pathogenic protein assemblies participate in many cellular processes. For instance, tau is involved in the stabilization of microtubules (Wang and Mandelkow, 2016). Monomeric Aβ peptides have neurotrophic and neuroprotective functions (Chasseigneaux and Allinquant, 2012). Huntingtin is involved in scaffolding, transport, and autophagy processes (Saudou and Humbert, 2016). α-Syn regulates synaptic transmission and calcium and mitochondrial homeostasis (Benskey et al., 2016). The aggregation of these proteins into mega-Dalton assemblies results in the loss of their cellular functions and the acquisition of deleterious properties (Ross and Poirier, 2004; Tyedmers et al., 2010.

Although made of proteins with different primary structures, pathogenic protein assemblies share several common properties. First, they form a continuum of oligomeric species ranging from dimers to fibrillar assemblies (Pieri et al., 2016). These fibrils could be straight, resembling needles, or, in other instances, be curved and twisted (Bousset et al., 2013). Second, aggregated pathogenic assemblies propagate from cell to cell and amplify themselves by recruiting soluble/monomeric proteins (Brundin et al., 2010). Third, pathogenic assemblies also share structural similarities within fibrils, where the constituting monomers are organized into parallel or anti-parallel, systematically hydrogen-bonded β sheets from which water molecules are excluded (Eisenberg and Jucker, 2012). When uncharged, the side chains extending from one β sheet interdigitate, like the teeth

of a zipper, with those extending from another β sheet. When charged, the side chains are exposed to the surface of the fibrillar core (Eisenberg and Jucker, 2012). Thus, the side chains generate surfaces characteristic for each fibrillar assembly.

The fibrillar protein assemblies associated with AD, PD, ALS, HD, and CJD differ by their surfaces because of differences in their primary structures. Differences in the surface of fibrils also exist for pathogenic assemblies made of one given protein, and they are referred to as strains (Melki, 2015). For a given pathogenic protein, different surface characteristics result from the conditions under which they formed. As a consequence, strains will have different biophysical properties and, likely, distinct interactomes. Interesting and in agreement with this view is the finding that fibrillar full-length and wild-type α-syn assemblies with distinct surfaces, although made of the same protein, yield different pathologies (Bousset et al., 2013; Peelaerts et al., 2015). Similar strain-dependent pathologies for mostly truncated tau assemblies (Kaufman et al., 2016; Sanders et al., 2014) and Aβ assemblies (Stöhr et al., 2014) have been reported. Although the concept of strains is very new for α-syn, Aβ, and tau, strain-dependent pathology has been long known and well documented for PrP^{RES} (Collinge and Clarke, 2007). Whether distinct surfaces of pathogenic protein assemblies and their location may account for the differences in their spatial and temporal route by which the pathology spreads within the brain remains an open question.

Pathogenic Protein Formation and Traffic

Aβ is an extracellular cleavage product of amyloid precursor protein, whereas α-syn and tau, HTTexon1, and SOD1 are intracellular proteins. Because of the predominantly extra-cellular localization of Aβ peptides, they can form aggregates, termed amyloid plaques, within the extracellular space when their local concentration exceeds the critical concentration for aggregate formation (Jucker and Walker, 2013). The concentration of all the other polypeptides listed above is high within axons, and, expectedly, they form intracellular aggregates. Several studies have demonstrated that α-syn, tau, and HTTexon1 are secreted from cells, independent of cell death, both in non-toxic monomeric form and toxic fibrillar forms (Kfoury et al., 2012; Brahic et al., 2016; Wu et al., 2016; Ren et al., 2009; Hansen et al., 2011; Takeda et al., 2015; Wegmann et al., 2016). The exact state of pathogenic assemblies outside of cells is still unclear, but both naked and membrane-encapsulated forms have been reported. This review neither covers the behavior of pathogenic assemblies within membranous compartments, because they may not directly interact with the plasma membrane components, nor the transfer of pathogenic assemblies via tunneling nanotubes, because this process bypasses the release and uptake pathways (Abounit et al., 2016; Tardivel et al., 2016). In the following sections, we will focus on the biophysical properties of pathogenic proteins following their release from one cell and binding to the plasma membrane of neighboring cells.

3D-to-2D Environmental Transition of Pathogenic Proteins

In 1905, Albert Einstein predicted that the random motions of molecules in a liquid would affect suspended particles, resulting in irregular, random motions of the particles or Brownian diffusion (Einstein, 1905; Box 1). The mode of diffusion in a biological environment is referred to as anomalous diffusion, which means that the mean square displacement of a molecule does not follow a linear relationship with time and is governed by size distribution of surrounding molecules, molecular density, and inter-molecular interactions (Bouchaud and Georges, 1990; Dix and Verkman, 2008; see Box 1 for definitions, equations, and figure). Protein mega-Dalton assemblies involved in diseases, such as Aβ, α-syn, tau, etc., are heterogeneous in nature and behave in a complex manner after their release in the extracellular space, where they exhibit 3D diffusion. The corresponding diffusion coefficients are difficult to predict because this will depend on their size, concentration, molecular density of the extracellular space, and the presence of partner molecules with which they may interact. Misfolded protein assemblies, naked or in complex with other secreted proteins, have to cross the extracellular matrix (ECM) environment to reach the "target" plasma membrane, where they may interact with proteins, lipid molecules, and/or membrane-associated ECM components (Figure 1). Then, after binding to the plasma membrane, the diffusion is restricted from 3D to a 2D diffusion in a crowded plane (see inset Figure B in Box 1). The reduced freedom of dimension available for diffusion increases the probability of molecular collisions with other proteins, including homologous ones, and then leads to the formation of clusters on the plasma membrane (Byström et al., 2008). This dynamic phenomenon has been observed for Aβ (Renner et al., 2010; Shrivastava et al., 2013; Ganzinger et al., 2014; Calamai et al., 2016) and α-syn (Shrivastava et al., 2015) assemblies.

It is difficult to estimate the volume explored by a given pathogenic protein in vivo after it has been released in the extracellular space, which corresponds to 15%–20% of the normal adult brain volume (Syková and Nicholson, 2008). When pathogenic protein assemblies are injected within a brain region, a 3D diffusion-dependent spread is seen around the injection site, and the spreading is proportional to the size of the protein assemblies (Rey et al., 2013; Selenica et al., 2013; Peelaerts et al., 2015; Shrivastava et al., 2015). However, at early disease stages, the amount of released misfolded protein assemblies is likely to be small, and they propagate along anatomically connected regions (Braak and Braak, 1991; Braak et al., 2003). This suggests the following sequence: a localized release of the deleterious protein assemblies at/around synapses, binding to the nearby synaptic plasma membrane, internalization in the adjacent neurons, and anterograde or retrograde transport with a possible amplification resulting from the recruitment and aggregation of endogenous soluble proteins. In case of *trans*-synaptic transfer, the distance to travel by means of 3D diffusion is small compared with that of the synaptic cleft, taking into account the space limitation by astroglia. Another but not exclusive possibility would be that pathogenic protein secretion/release and uptake would take place at a distance from synaptic sites that involve binding and uptake at adjacent or neighboring cell membranes. Anyhow, the propagations involve neuron-to-neuron and/or neuron-to-glial transfer (Pearce et al., 2015). The next sections will focus on various biomolecules that may contribute to the binding of pathogenic proteins on the external surface of neurons and the biophysical consequences of these interactions.

Box 1. Definitions of Terms Associated with the Diffusion of Pathogenic Proteins

DIFFUSION

Dispersion from one region of space to another resulting from random movements of particles. Pathogenic proteins diffuse randomly in the 3D extracellular space (3D) and bind to the plasma membrane, where they diffuse in the 2D plane. During diffusion, they may bind to or unbind from various proteins/lipids.

SINGLE-PARTICLE TRACKING

Monitoring the movements of fluorescently labeled particles (e.g., proteins) at a single-molecule level, allowing the determination of characteristic physical properties. The diffusion behavior of single pathogenic proteins can be visualized using tagged assemblies. The label can make use of the biotin-streptavidin complex for quantum dot-based tracking, photo-convertible dyes (such as Dendra2 and mEos; Li et al., 2016) for super-resolution PALM-based tracking, or fluorescent antibodies (fragment antigen-binding [F_{ab}] or nanobodies) for universal point accumulation for imaging in nanoscale topography (uPAINT) (Chamma et al., 2016).

DIFFUSION COEFFICIENT

The surface area explored per unit time by a diffusing particle. The diffusion coefficient (D) is a physical characteristic that will depend on the size of diffusing molecules, the physical properties of the surrounding environment, temperature, and pressure. In biological systems, it is an effective diffusion coefficient that depends on local viscosity and molecular interactions. This is why a broad range of diffusion coefficients (10^{-4}–10 $\mu m^2/s$) is observed for pathogenic proteins when diffusing on the plasma membrane. As expected, a larger protein complex (e.g., an aggregate) will diffuse slower than a smaller complex. The value of the diffusion coefficient is computed using mean square displacement values (MSD, see below).

MSD

MSD is defined as the square of the displacement of a particle at a given time relative to the position of the particle at zero time, averaged over many particles (Dix and Verkman, 2008). The shape of the MSD versus time curve forms the basis of classification of different modes of diffusion, such as Brownian/normal or anomalous or directed diffusion (Figure A).

CHARACTERIZATION OF DIFFUSION BEHAVIOR BASED ON MSD

Normal or Brownian diffusion: The diffusion of particles in a homogeneous solution where the size of the diffusing particle is comparable with other molecules in the solution. The primary determinants of diffusion of a given particle are the particle size and shape. Because of local heterogeneities of biological systems, Brownian diffusion is only an approximation. For Brownian diffusion, MSD (r^2) follows a linear relation with time (Figure A, blue trace). The MSD (r^2) of a particle is related to the dimension of diffusion (2D or 3D) by the following equations (Saxton and Jacobson, 1997):

$$r^2 = 6Dt \text{(3-dimensional diffusion)}$$
$$r^2 = 4Dt \text{(2-dimensional diffusion)}$$

Anomalous diffusion: Biomolecules diffuse in a non-homogeneous environment, with particles (e.g., proteins) of various sizes and shapes present in the solution, within a volume or surface having heterogeneous properties (Figure A, green trace). On the plasma membrane, pathogenic proteins exhibit anomalous diffusion behavior. This is because pathogenic proteins encounter both resident membrane proteins/lipids and other pathogenic proteins with which they interact and/or collide. The inter-molecular collisions and interactions within the membrane prevent Brownian behavior. For anomalous diffusion, the MSD (r^2) of a particle is related to D by the following equations (Saxton and Jacobson, 1997):

$$r^2 = 6Dt^{\alpha} \text{(3-dimensional diffusion)}$$
$$r^2 = 4Dt^{\alpha} \text{(2-dimensional diffusion)}$$

α is a measure of non-linearity. Typically, on the plasma membrane, $\alpha < 1$, and the diffusing behavior is qualified as anomalous sub-diffusion.

(Continued on next page)

Box 1. *Continued*

DIRECTED DIFFUSION

A particle follows directed motion; for example, when bound to cytoskeletal structures through molecular motors, it moves with a given velocity along one direction (Figure A, red trace). It also diffuses over a short distance in the perpendicular direction because of the flexibility of the cytoskeletal element, or it diffuses isotropically over short distances from its attachment point because of the flexibility of the attachment (Saxton and Jacobson, 1997). This type of diffusion is observed when a pathogenic protein is bound to vesicles following endocytosis and anterogradely/retrogradely trafficked along microtubules. The MSD (r^2) of a particle, for a velocity, V, is related to D by the following equation:

$$r^2 = 4Dt^{\alpha} + (Vt)^2 \text{ (2-dimensional diffusion)}$$

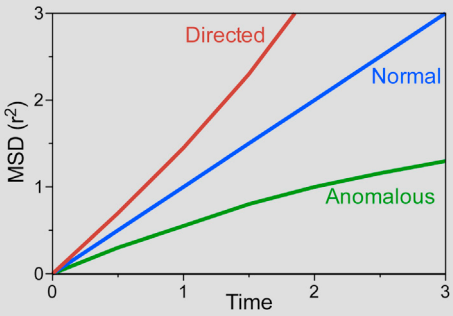

Figure A. Shown is a plot of MSD (r2) versus time (adapted from Saxton and Jacobson, 1997) for normal (Brownian) diffusion, anomalous diffusion (downward-bent), and directed diffusion (upward-bent) diffusion.

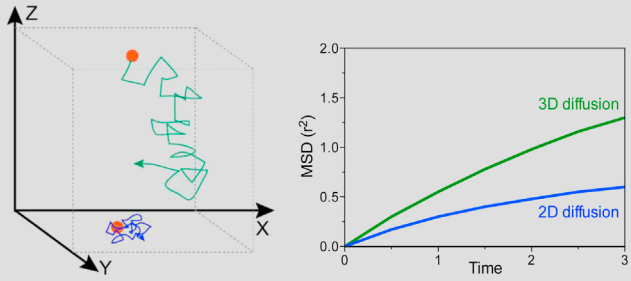

Figure B. Transition of Diffusing Pathogenic Proteins from 3D to 2D.

Shown are trajectories of a pathogenic protein diffusing in 3D (green) or 2D (blue) space (left). The orange spot depicts the point of origin (for example, release site). In 3D and non-infinite time intervals, the probability for a random walk to never return to its starting point is certain (Ben-Naim et al., 2008). In 2D, a randomly diffusing trajectory is certain to return to its starting point in a given time interval and depends mainly on the diffusion coefficient. The MSD versus time plot (right) for a pathogenic protein in the 3D extracellular space has the characteristic of anomalous diffusion because of heterogeneous viscosity of the extracellular space in which it travels. When interacting with the plasma membrane plane, the diffusion of the same protein will be restrained to a 2D space. Here the anomalous diffusion displays increased confinement (blue curve, downward shift) resulting from the crowded environment (Saxton and Jacobson, 1997). The reduction of the volume available for diffusion forms extracellular space (3D), so the cell surface (2D) increases the probability of molecular encounters at the plasma membrane, which, consequently, acts as a chemical reactor.

Pathogenic Protein Interactions with the Plasma Membrane

Pathogenic protein assemblies bind to a large number of molecules at the cell surface (Figure 1; Table 1). Although they do not have "specific receptors" and interact with many membrane-associated molecules and diverse protein assemblies, their distinct surface properties exhibit different affinities for molecules at the cell surface. They cluster on the plasma membrane of neuronal and non-neuronal cell types and trigger deleterious consequences resulting from protein assemblies that drive changes in lipid bilayer fluidity, membrane architecture, and the normal distribution of membranous proteins. Several plasma membrane and membrane-associated components (proteins, lipids, and ECM) affect and/or contribute to the interaction of

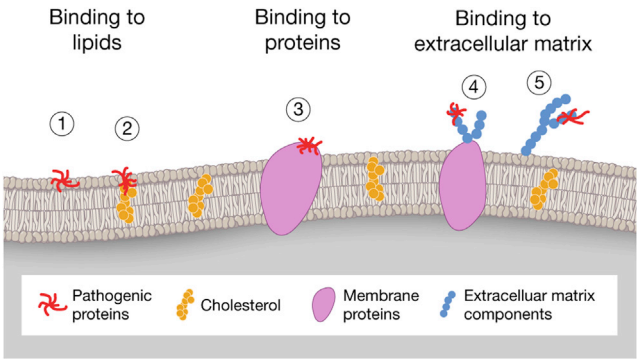

Figure 1. Binding Partners of Pathogenic Proteins
Pathogenic proteins may bind to various biomolecules on the plasma membrane. This includes lipids (1) and cholesterol (2), receptors and channels (3), and ECM components, including glycoproteins (4) or carbohydrate chains (5). Also see Table 1 for known pathogenic protein binding partners.

misfolded protein assemblies, whether naked or in complex with other secreted proteins (Table 1).

Interactions with the ECM Components

Both the type and net charge of the ECM components and the size and net charge of the misfolded protein assemblies contribute to their binding and further aggregation. ECM components may act as a barrier restricting access to the plasma membrane: neurons with abundant ECM components are devoid of neurofibrillary tangles of tau in AD (Brückner et al., 1999; Härtig et al., 2001; Morawski et al., 2010) and are protected against Aβ neurotoxicity (Miyata et al., 2007). The implication of ECM components has been reinforced by recent studies using mice lacking aggrecan (chondroitin sulfate proteoglycan), cartilage link-protein 1 (stabilizing the interaction between hyaluronic acid and proteoglycans such as aggrecan), or tenascin-R (extracellular glycoprotein) (Suttkus et al., 2016). Mouse knockout for any of the three components increased the internalization of tau protein and, consequently, increased tau spreading (Suttkus et al., 2016). Other glycoproteins, such as reelin (secreted protein), were shown to protect neurons by binding soluble Aβ species, thus delaying fibril formation and preventing spine loss (Pujadas et al., 2014).

In contrast, ECM components such as proteoglycans containing heparan sulfate side chains (HSPGs) promote the binding and internalization of misfolded protein assemblies, including PrP (Horonchik et al., 2005), tau, and α-syn (Holmes et al., 2013) or Aβ (Kanekiyo et al., 2011). Although agrin and glypicans were identified in a proteomics screen with fibrillar α-syn assemblies (Shrivastava et al., 2015), the implication of specific HSPGs remains unclear. Apart from contributing to Aβ assemblies binding to cells, HSPGs also promote the conversion of non-fibrillar amyloid Aβ into neurotoxic fibrillar forms in AD. HSPGs, including agrin and glypicans, are associated with senile plaques in the brain of human AD patients (Verbeek et al., 1999; van Horssen et al., 2002). Agrin also binds to α-syn in a heparan sulfate-dependent manner, induces conformational changes, and favors aggregation (Liu et al., 2005). In the same line, agrin co-localizes with Lewy bodies in the substantia nigra in the PD brain (Liu et al., 2005). Altogether, these data indicate that HSPGs not only contribute to the binding of misfolded protein assemblies but also promote their aggregation. It is plausible that, although agrin-HSPG promotes fibrillization, another unknown HSPG promotes internalization. A recent study showed that hyposialylation favors the cellular uptake of Aβ (Bosch-Morató et al., 2016). A clearer picture of the structure, function, and distribution of the ECM is still emerging, but, based on these studies, it appears that chondroitin-sulfated proteoglycans may safeguard neurons from pathogenic proteins, whereas heparan-sulfated proteoglycans increase neuronal vulnerability.

Interactions with Lipid Components

Direct interactions of misfolded protein assemblies with the outer lipid leaflet of the plasma membrane contribute to their binding to cells. For instance, Aβ assemblies interact with cholesterol (Avdulov et al., 1997; Di Scala et al., 2014) and with gangliosides (Yanagisawa et al., 1995; Molander-Melin et al., 2005), a class of amphiphilic glycolipids at the external membrane leaflet exposing oligosaccharide chains toward the exterior of the cell. Further aggregation of Aβ assemblies occurs on interaction with cholesterol (Avdulov et al., 1997) and the ganglioside GM1 (Hong et al., 2014). In the same line, α-syn assemblies interact with negatively charged phospholipids (Pieri et al., 2012), cholesterol, and gangliosides (Fantini and Yahi, 2011, 2013; Fantini et al., 2011) on the outer leaflet of the plasma membrane. The binding of α-syn assemblies to lipids is further supported by single-particle tracking on the neuron surface showing high diffusion speed and long trajectories (Shrivastava et al., 2013) with features similar to those of lipids (Renner et. al., 2009) prior to their clustering. Similarly, tau protein and huntingtin interact with phospholipids (Jones et al., 2012; Patel et al., 2015; Pieri et al., 2012; Burke et al., 2013), and huntingtin was also found to be associated with lipid raft-enriched, detergent-resistant membranes (Valencia et al., 2010).

Interactions with Membrane Proteins

Direct interaction of misfolded protein assemblies with membrane proteins has received significant attention since pharmacological and genetic tools allow manipulation of such interactions. Membranous PrP^{C} (cellular prion protein) interacts with aggregated PrP; e.g., PrP^{RES} (Aguzzi and Falsig, 2012). A recent study identified PrP^{C} as a ligand for the G protein-coupled receptor Gpr126 in Schwann cells (Küffer et al., 2016). Although Gpr126 is not expressed in neurons, this study indicates that neuronal PrP^{RES} may not only bind to PrP^{C} but also acts as a ligand for other neuronal G protein-coupled receptors such as mGluR5s, which physically interact with PrP^{C} (Um et al., 2013). Several membrane proteins (Table 1) have been shown to interact with Aβ assemblies (Jarosz-Griffiths et al., 2016). Just to mention some of these interactions, Aβ assemblies bind with high affinity to α7-nicotinic acetylcholine receptors (Wang et al., 2000; Dineley et al., 2001; Snyder et al., 2005; Dziewczapolski et al., 2009), leukocyte immunoglobulin-like receptor B2 (Kim et al., 2013), α3-Na^{+}/K^{+}-ATPase (α3-NKA) (Ohnishi et al., 2015), Ephrin B2 receptor (EphB2) (Cissé et al., 2011a), and the PrP^{C}-mGluR5 complex (Laurén et al., 2009; Renner et al., 2010; Um et al., 2013; Haas et al., 2014, 2016; Hu et al., 2014). Among these, because of available pharmacological agents, Aβ interaction with PrP^{C}-mGluR5 has received much attention. Although PrP^{C} knockout does not abolish Aβ binding

Table 1. Binding Partners of Pathogenic Proteins on the Neuronal Cell Membrane

	Pathogenic Proteins			
	Prion Proteins	Amyloid β	α-Synuclein	Tau
ECM components	HSPGs (Caughey et al., 1994)	HSPGs (Fraser et al., 1992)	HSPGs (Cohlberg et al., 2002)	HSPGs (Goedert et al., 1996)
	(Horonchik et al., 2005)	(Kanekiyo et al., 2011)	(Holmes et al., 2013)	(Holmes et al., 2013)
	Glypican-1 (Taylor et al., 2009)	Perlecans (Castillo et al., 1997)	Agrin (Liu et al., 2005)	
		Glypican-1 (Watanabe et al., 2004)		
		Agrin (Cotman et al., 2000)		
		Reelin (Pujadas et al., 2014)		
Lipids		cholesterol (Avdulov et al., 1997)	cholesterol (Fantini et al., 2011)	
		ganglioside GM1 (Yanagisawa et al., 1995)	ganglioside GM1 (Martinez et al., 2007)	
			ganglioside GM3 (Di Pasquale et al., 2010)	
Membrane proteins	PrP^c (Brandner et al., 1996)	RAGE (Yan et al., 1996)	α3-Na^+/K^+-ATPase (Shrivastava et al., 2015)	muscarinic M1 and M3 receptors (Gómez-Ramos et al., 2008)
	Adgrg6 (Küffer et al., 2016)[a]	p75 neurotrophin receptor (Yaar et al., 1997)	LAG3 (Mao et al., 2016)	
		α7-nAChR (Wang et al., 2000)	Neurexin subunits[b]	
		insulin receptor (Xie et al., 2002)	1α/2α (Shrivastava et al., 2015)	
		Frizzled (Magdesian et al., 2008)	1β/2β/3β (Mao et al., 2016)	
		PrP^c (Laurén et al., 2009)		
		AMPA receptors (Zhao et al., 2010)		
		mGluR5 (Renner et al., 2010)		
		β2-adrenergic receptor (Wang et al., 2010)		
		EphB2 (Cissé et al., 2011a)		
		Neuroligin 1 (Dinamarca et al., 2011)		
		Amylin-3 receptor (Fu et al., 2012)		
		FcγRIIb (Kam et al., 2013)		
		PirB/LilrB2 (Kim et al., 2013)		
		EphA4 (Vargas et al., 2014)		
		Sigma-2/PGRMC1 receptors (Izzo et al., 2014)		
		α3-Na^+/K^+-ATPase (Ohnishi et al., 2015)		
		Neurexin subunits		
		2α (Brito-Moreira et al., 2017)		
		1β/2β/3β (Naito et al., 2017)		

Adgrg6, adhesion G protein-coupled receptor G6 or GPR126; α3-Na^+/K^+-ATPase, α3 subunit of sodium potassium ATPase; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; EphB2/A4, Ephrin B2/A4 receptor; FcγRIIb, Fcγ receptor II-b; LAG3, lymphocyte activation gene 3; mGluR5, metabotropic glutamate receptor type 5; nAChRs, nicotinic acetylcholine receptors; PirB/LilrB2, paired immunoglobulin-like receptor B/leukocyte immunoglobulin-like receptor B2; PrP^c, cellular prion protein; RAGE, receptor for advanced glycation end products.
[a]Identified as Schwan cell receptor that binds to a fragment of neuronal PrP^c.
[b]Identified in screen but requires verification.

to cells and subsequent neurotoxicity (Balducci et al., 2010; Calella et al., 2010; Kessels et al., 2010; Cissé et al., 2011b), knocking down mGluR5s (Hamilton et al., 2014) and pharmaceutical inhibition of mGluR5s (Um et al., 2013; Hamilton et al., 2016) delay neurodegeneration significantly. This suggests that mGluR5s is the critical membranous partner for Aβ pathologic

Box 2. Membrane-Driven Misfolded Protein Aggregation

Proteins in general and natively unfolded polypeptides in particular adopt numerous conformations. Let us assume that each amino acid residue can adopt three conformations (one *trans* and two gauche) with two torsion angles within a natively unfolded polypeptide made of 100 amino acid residues. The number of conformations such a polypeptides could adopt would be 3^{99x2}; i.e., 10^{95} possible conformations. The concentration and lifespan of each conformer are characteristic of the precise conformation the polypeptide adopts. The amino acid stretches exposed at the surface of a given conformer define its association and dissociation constants with different membrane components. The reversible binding of defined conformers with cell membrane components favors those conformations by displacement of the equilibria between the different conformers in solution toward those that bind with the highest affinity to membrane components. Thus, membrane components operate a triage between numerous conformers. When aggregation-prone conformations are populated by specific selection through binding to membrane components, further binding may either be negative (when the binding of one molecule opposes the binding of others) or positive (when the binding of one molecule facilitates the binding of others). Unless binding is negative, the local concentration of aggregation-prone conformers increases, favoring cooperative aggregation.

assemblies. Co-localization of Aβ oligomers and mGluR5s were also observed on astrocytes in mice and humans (Casley et al., 2009; Lim et al., 2013; Shrivastava et al., 2013).

A comparable mechanism was found for α-syn assemblies, which interact with the neuron-specific α3 subunit of the sodium pump NKA (Shrivastava et al., 2015). Another study showed that binding of α-syn fibrils to membrane protein lymphocyte activation gene 3 (LAG3) contributes to α-syn endocytosis and cell-to-cell transmission and toxicity (Mao et al., 2016). Assemblies of α-syn also bind to other membrane proteins; e.g., neurexin subunits (Shrivastava et al., 2015; Mao et al., 2016), amyloid β precursor-like protein 1 (Mao et al., 2016), and the glucose-related protein of 78 kDa (GRP78; Bellani et al., 2014). Finally, extracellular tau assembly interaction with muscarinic receptors has been reported (Gómez-Ramos et al., 2008).

Thus, misfolded protein assemblies may interact with ECM components (HSPGs and glycoproteins), outer membrane lipids (cholesterol and gangliosides), and membranous proteins (Table 1). This diversity of partners suggests that there is no specific "receptor" for misfolded protein assemblies. The availability of multiple binders within the plane of the plasma membrane suggests that these multiple interactions increase pathogenic protein density, thus promoting 2D diffusion-dependent inter-molecular interactions inducing clustering and subsequent toxicity.

Consequences of Pathogenic Protein Binding to the Cell Membrane

Single-particle tracking and high-resolution imaging approaches have shed new light on the fate of misfolded protein assemblies after binding to the plasma membrane. The clustering of pathogenic proteins on the plane of the membrane results in the redistribution and trapping of membrane proteins and lipid molecules by a so-called diffusion trap mechanism comparable with that described for the interaction between receptors and scaffolding proteins and their subsequent accumulation at synapses (Triller and Choquet, 2008).

Changes in the Biophysical Properties of Pathogenic Proteins

In a manner similar to native functional proteins, misfolded proteins oscillate between different shapes, exposing diverse amino acid residues and surfaces (Fersht, 1999). This allows longitudinal and/or lateral interactions between like molecules, leading to fibril formation (Eisenberg and Jucker, 2012; Brundin et al., 2010). Metastable pre-fibrillar oligomeric precursors form in the early stages of assembly into fibrils (Goldberg and Lansbury, 2000; Lashuel et al., 2002). To date, an extremely large variety of oligomeric species that differ in structure, molecular weight, and morphology have been described (Danzer et al., 2007; Cremades et al., 2012; Qin et al., 2007; Ehrnhoefer et al., 2008; Zhou et al., 2010; Pieri et al., 2016). In addition, the distinct conformation a pathogenic protein may adopt through its "chameleon" property in solution (Uversky, 2003) allows interactions with membrane components with different affinities. The interaction of misfolded proteins and their assemblies with membrane components restricts the conformational states they explore in solution (Onuchic et al., 1996). This is achieved by displacing the equilibrium between the different conformations they may adopt toward the one with the highest affinity for membrane components. Thus, for any given protein involved in neurodegenerative diseases, binding to membrane components selects specific conformations of the many they can adopt. In addition, the diffusion-dependent interaction of misfolded proteins and their assemblies with membranous components increases their local concentration. This is due to the shift from 3D to 2D diffusion. The subsequent molecular crowding increases the probability to reach a critical concentration, above which thermodynamically stable misfolded protein assemblies form and further grow in an unlimited manner (Oosawa and Asakura, 1975). Distinct membrane component-mediated selection of different protein conformers/oligomers together with the diffusion-dependent increase in protein conformer/oligomer concentration may be at the origin of the aggregation of a given protein into strains; e.g., structurally and functionally distinct assemblies. Overall, the plasma membrane sorts misfolded assemblies in a way that may favor selected pathogenic conformations and promote molecular clustering/aggregation (Box 2).

Lateral Diffusion and Aggregation of Pathogenic Proteins

Whether interacting with membrane-bound ECMs, lipid molecules, or membranous proteins, misfolded proteins and their assemblies exhibit anomalous diffusion along the plane of the membrane (Renner et al., 2010; Shrivastava et al., 2013, 2015). While diffusing, misfolded protein molecules and/or their assemblies may encounter identical molecules, resulting

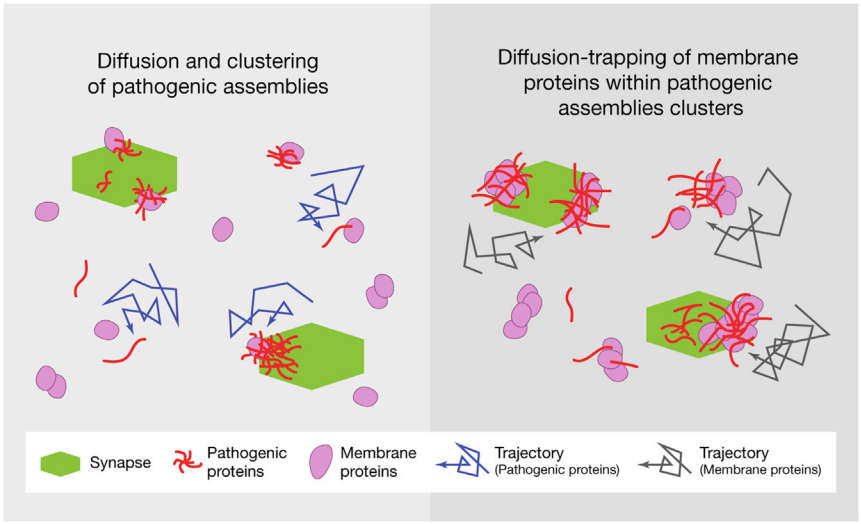

Figure 2. The Plasma Membrane Acts as a Chemical Reactor: It Favors Interactions between Proteins and the Formation of Clusters

Following binding to the plasma membrane, pathogenic proteins diffuse along the 2D plane that will favor interaction (also see Box 1) with other proteins (other pathogenic proteins and membrane receptors; Table 1). Left: interactions between pathogenic proteins promote their aggregation, often observed in the vicinity of synapses. Right: the aggregates of pathogenic proteins will trap diffusing native membrane components, resulting in the formation of clusters. Thus, the presence of non-physiological aggregates of pathogenic proteins can alter the distribution and function of physiologically important membrane proteins such as receptors, channels, or pumps (from left to right).

in interaction-driven aggregation, which, in turn, may induce abnormal or pathogenic distribution of partner membranous components (discussed below in Trapping and Clustering of Membrane Proteins). Thus, by restricting the space of diffusion from 3D to 2D, the plasma membrane acts as a chemical reactor (Figure 2; Salvatico et al., 2015), favoring molecular interactions. A good example is that of Aβ oligomers, the aggregation of which increases on 2D charged membranes with the amount of charged lipids, consequently forming toxic aggregates because of molecular crowding (Bokvist et al., 2004; Bokvist and Gröbner, 2007). A recent study highlights the biological relation of membrane aggregation to toxicity for Aβ assemblies using mouse models where Aβ was either membrane-anchored or non-anchored (Nagarathinam et al., 2013). Membrane-anchored but not non-anchored Aβ-accelerated Aβ deposition exacerbated amyloid-associated toxicity upon crossing with Aβ precursor protein transgenic mice (Nagarathinam et al., 2013). This study established that chronic association of Aβ peptides with the plasma membrane accelerates neurodegeneration. This is in line with work suggesting that the plasma membrane is the initial site for plaque deposition in human AD patients (Yamaguchi et al., 2000) as well as in a rodent model (Kokubo et al., 2005). In the case of α-syn, the oligomeric form shifts from a mono- to poly-dispersed structures in the presence of phospholipid membranes (Anunciado et al., 2015). Accordingly, the clustering of α-syn assemblies on the neuronal plasma membrane has been shown with super-resolution microscopy (Shrivastava et al., 2015). Using electron microscopy, another study reported that plasma membrane-bound fibrils of α-syn serve as nucleation sites for the aggregation and conversion into amyloid-like structures for extracellular monomeric α-syn (Mahul-Mellier et al., 2015). In the case of PrP^{RES} conversion, replication, and aggregation, the role of membranes has also been established. The lipid-rich domains on the plasma membrane are the sites for PrP^{RES} aggregation and rapid conversion (Goold et al., 2011; Godsave et al., 2013; Rouvinski et al., 2014). Furthermore, in vivo studies identified plasma membrane invaginations with PrP^{RES} aggregates as an early sign of prion disease (Godsave et al., 2013). In addition, PrP^{RES} remained on the cell surface for hours, in the form of slow-moving strings and webs, sheltered from endocytosis (Rouvinski et al., 2014).

Pore Formation

The crowding at the plasma membrane rises with the increasing concentration of misfolded protein assemblies. This, together with the clustering and further aggregation of misfolded protein assemblies into higher-order structures ranging from pore-like to raft-like structures (Danzer et al., 2007; Kayed et al., 2003, 2004; Kostka et al., 2008), has consequences on overall membrane overall integrity, physical properties, and geometry (Antonny 2011; Garten et al., 2015; Milanesi et al., 2012; Li and Gorfe, 2014).

Trapping and Clustering of Membrane Proteins

Following their diffusion, both Aβ and α-syn assemblies form clusters in the vicinity of synapses (Renner et al., 2010; Shrivastava et al., 2015). The preferential clustering of misfolded protein assemblies around curved membranous structures such as synapses could be either due to their higher affinity for defined membrane geometry (Pranke et al., 2011) or due to protein partners within these structures. In any case, the clustering of misfolded proteins affects the dynamic properties of both their membranous partners and the membrane geometry. The reduced dynamics and/or trapping of misfolded proteins partners, ECM, and lipids leads to aberrant, non-physiological distribution and, eventually, pathological gain or loss of signaling functions (Figure 2; Calamai and Pavone, 2013; Calamai et al., 2016; Ganzinger et al., 2014; Hong et al., 2014; Ross and Poirier, 2004; Renner et al., 2010; Shrivastava et al., 2013, 2015; Yu et al., 2014).

The increased localization of mGluR5s following diffusion trapping by Aβ assemblies at excitatory synapses and, more specifically, at dendritic spines (Figure 3) results in a constitutively activated signaling platform (gain of function) characterized by an increased mGluR5s-dependent Ca^{2+} response (Renner et al., 2010). The increased Ca^{2+} response is either the consequence of Aβ assemblies directly activating mGluR5s or PrP^{C}-mediated activation of mGluR5s (Um et al., 2013; Haas et al., 2014, 2016; Hu et al., 2014). The non-physiological misfolded

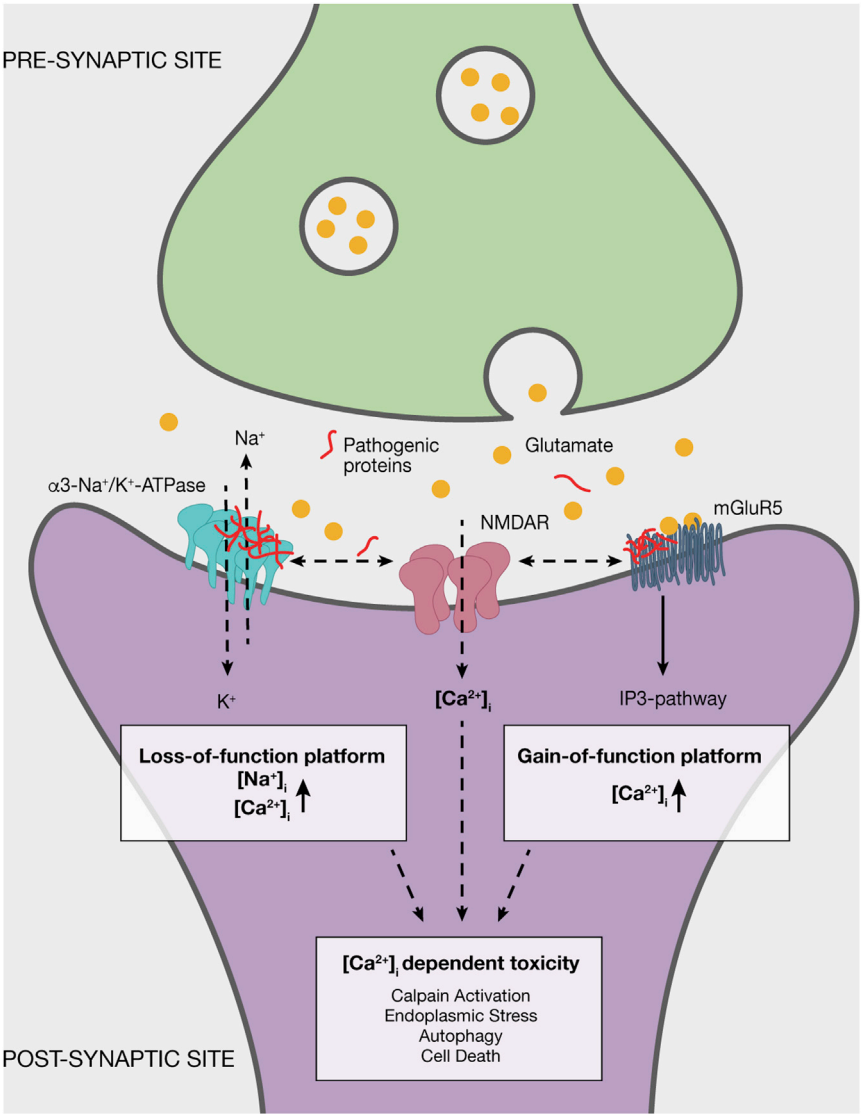

Figure 3. Deleterious Effects at Excitatory Synapses following Pathogenic Assembly Interaction with Membrane Proteins

Following their binding and clustering in the vicinity of synapses, pathogenic proteins initiate deleterious effects by forming artificial signaling platforms. This can be a loss-of-function platform (e.g., α-syn/α3-NKA; Shrivastava et al., 2015) or gain-of-function platform (e.g., the Aβ/mGluR5 complex; Renner et al., 2010). These platforms alter the ionic gradient in neurons by compromising the activity of trapped membrane proteins. The functional coupling of α3-NKA/mGluR5s with NMDA receptors indirectly alters the activity of the latter, resulting in Ca^{2+}-dependent toxicity.

protein-mediated redistribution of partners within the membrane can also mimic the loss of function of a signaling pathway, observed following Aβ- and α-syn-mediated re-distribution of the α3-NKA (Figure 3; Ohnishi et al., 2015; Shrivastava et al., 2015). Similarly, Aβ assembly-mediated GM1 clustering (Calamai and Pavone, 2013; Hong et al., 2014) will affect the maintenance of raft-like domains and membrane viscosity (Eggeling et al., 2009; Renner et al., 2009).

Changes in the Topography of the Plasma Membrane

Misfolded protein binding, lateral diffusion, and further aggregation within the plasma membrane and misfolded protein-mediated redistribution of membranous partner molecules remodel the topography and fluidity of the plasma membrane. The changes range from alteration in membrane outer leaflet lipid composition because of the extraction of lipids from the lipid bilayer (Pandey et al., 2009; van Rooijen et al., 2009; Reynolds et al., 2011; Hellstrand et al., 2013) to the stiffening of the plasma membrane to the point where its integrity is compromised following rupture (Varkey et al., 2010; Pieri et al., 2012)

Alterations in Synaptic Scaffold Composition

Membrane receptors are stabilized at synapses by their interaction with sub-membranous scaffold proteins. A synapse can be described as a three-layer structure: a membrane, a sub-membrane, and a bulk layer (Sekimoto and Triller, 2009). This layered organization at the postsynaptic region is maintained through reciprocal interactions where scaffold proteins stabilize synaptic receptors that, in turn, stabilize scaffold proteins (Sekimoto and Triller, 2009). A similar mutual stabilization process may occur when pathogenic assemblies interact with partner molecules. Such interactions may subsequently lead to alteration of the sub-membrane proteins and their interacting partners' organization. A recent example of such a mechanism is that of PTEN (phosphatase and tensin homolog)-altered accumulation in spine heads following exposure to Aβ assemblies (Knafo et al., 2016). The recruitment of PTEN is likely to result from an increased association of PTEN with PSD-95 via a PDZ domain-dependent interaction (Knafo et al., 2016). Although speculative, the underlying mechanism may involve a liquid-liquid phase separation mechanism, which has been recently proposed in an unrelated study (Zeng et al., 2016)

Physiological Changes because of Misfolded Protein Assembly-Mediated Clustering of Partner Proteins

Glutamate Receptors Activation

Excessive influx of Ca^{2+} disrupts ion homeostasis, cell metabolism, and initiates the activation of apoptotic and necrotic pathways. Indeed, the intracellular Ca^{2+} ($[Ca^{2+}]_i$) level regulates the number and composition of receptors/channels in and outside of synapses (Choquet and Triller, 2013). Thus, the clustering of pathogenic proteins and membrane receptors around

the excitatory synapses will affect glutamate receptor signaling by constraining the flux of glutamate receptors in and out of synapses. In addition, functional coupling of glutamate receptors, specifically N-methyl-D-aspartate (NMDA) receptors with several synaptic receptors, such as mGlu5Rs (Rammes et al., 2011), α3-NKA (Akkuratov et al., 2015), EphB (Nolt et al., 2011; Cissé et al., 2011a), etc., could impair NMDA receptor function and, consequently, long-term potentiation in neurodegenerative diseases (Shankar et al., 2007; De Felice et al., 2007; Cissé et al., 2011a; Li et al., 2011; Rammes et al., 2011; Diógenes et al., 2012; Hu et al., 2014).

The metabotropic glutamate receptors, specifically mGluR5s, also contribute to a rise in $[Ca^{2+}]_i$, which can be deleterious for neurons. The exposure of neurons to Aβ oligomers induces mGluR5-dependent release of Ca^{2+} from the endoplasmic reticulum and, consequently, toxicity (Renner et al., 2010; Um et al., 2013). Similarly, in astrocytes, Aβ oligomers cluster mGluR5, leading to an increase in $[Ca^{2+}]_i$ (Lim et al., 2013; Shrivastava et al., 2013). Thus, the mGluR5 platforms resulting from clustering lead to a gain of function and contribute to the deleterious effects of Aβ oligomers. In PD, mGluR5 antagonists are neuroprotective, but their mechanism of action remains unclear (Morin et al., 2013). Co-localization and co-immunoprecipitation of mGluR5s with α-syn has been reported in the hippocampus (Price et al., 2010; Overk et al., 2014). Furthermore, increased expression of mGluR5s has been reported in PD patient brains (Sanchez-Pernaute et al., 2008; Price et al., 2010). Notably, an upregulation of mGluR5s has been observed not only in PD and AD but several other neurodegenerative disorders. The upregulation, increased clustering, and increased surface expression of mGluR5 in neurons and astrocytes could be part of a neuroinflammatory response dependent on extracellular ATP/adenosine concentration (Pascual et al., 2012; Shrivastava et al., 2013), but this needs further evaluation. In any case, the increased surface availability of mGluR5s and its deleterious clustering is likely at the origin of elevated $[Ca^{2+}]_i$. High $[Ca^{2+}]_i$ will trigger calpain activation, endoplasmic reticulum stress, increased autophagy, and cell death (Figure 3; Mattson, 2007).

Impairment of Ion Transporters

Both Aβ (Ohnishi et al., 2015) and α-syn (Shrivastava et al., 2015) interact with the α3 subunit of the NKA and impair the function of this pump. Remarkably, both Aβ and α-syn were found to bind to the same amino acid stretch centered on asparagine (Asn^{879}) that is located in the third extracellular loop of the α3 subunit of NKA. The binding of Aβ oligomers to α3-NKA was reported to impair its catalytic activity, measured as ATP hydrolysis (Ohnishi et al., 2015). The binding of α-syn to α3-NKA was reported to decrease the capacity of the transporter to rapidly extrude sodium ions because of aberrant co-clustering around synapses. Both interactions were found to increase Ca^{2+} excitotoxicity (Figure 3).

NKA restores the intracellular ion imbalance following action potential propagation by transporting three Na^+ out of and two K^+ into the cell at the expense of one molecule of ATP. The minimal functional unit of NKA is a dimer, consisting of a catalytic α subunit and a β subunit; the latter is required for the insertion of NKA into the membrane (Kaplan, 2002). Neurons express two isoforms of the catalytic α subunit: the ubiquitous α1 and the neuron-specific α3. The neuron-specific isoform has a lower affinity for Na^+ than the ubiquitous α1 isoform and is in a better position to take care of large transient increases in intracellular Na^+ during high neuronal activity (Azarias et al., 2013). The α3 subunit also plays a pivotal role in the dynamic control of membrane potential. The brain is dependent on a functional NKA α3 subunit. Mutations in the α3 subunit have been described in several rare diseases (Heinzen et al., 2014) with severe neurological disturbances, and recently it has been reported (Ruegsegger et al., 2016) that the intracellular interaction between the α3 subunit and the ALS-associated human mutant of SuperOxide Dismutase (SOD) accounts for some of the ALS symptoms. Furthermore, in the healthy brain, NKA activity accounts for approximately 50% of total brain energy consumption (Harris et al., 2012). Mitochondrial dysfunction is a common feature in genetic and sporadic PD, and mitochondrial dysfunction has also been shown to play an important role in the pathophysiology of AD (Johri and Beal, 2012). Based on the recent findings that α-syn and Aβ assembly binding to the extracellular domain of the neuronal α3 isoform of NKA is deleterious, one can speculate that these neurodegenerative diseases are associated with a brain energy crisis where both the supplier and the processor of the energy are at stake.

Therapeutic Perspectives

The prion-like effects of Aβ, α-syn, and other pathogenic proteins offer alternative therapeutic strategies. Targeting extracellular and/or membrane-bound pathogenic assemblies and/or their interaction partners could prevent some of the early deleterious steps that lead, with time, to neurodegeneration. A first approach based on the inhibition and/or reduction of pathogenic protein assembly binding to the membrane should diminish their ability to further assemble and reorganize into toxic macromolecular structures. It could also prevent alterations in membrane components' dynamics and clustering. A second approach relying on the pharmacological modulation of the activity of plasma membrane proteins interacting with pathogenic assemblies would provide an additional therapeutic tool that would provide rescue from the downstream effects of deleterious signaling.

Disrupting Pathogenic Protein Binding to the Plasma Membrane

The clustering of pathogenic proteins and their assemblies within the cell membrane can indeed generate protein scaffolds that actively recruit other neuronal membrane proteins and compromise their function or normal distribution. Alternatively, the binding and docking of pathogenic protein assemblies may affect the overall normal distribution of membrane proteins through a passive exclusion mechanism, leading to a pathologic distribution. Understanding these changes is a prerequisite for a therapeutic strategy aimed at restoring the normal protein distributions. Recent studies have demonstrated that the binding of ligands (such as hsc70) to pathogenic protein assemblies can affect their ability to interact with the plasma membrane components, resulting in decreased toxicity (Pemberton et al., 2011). One cannot fully prevent the binding of pathogenic assemblies to the neuronal membrane. However, reducing the concentration of unbound assemblies within the extracellular milieu is eventually doable by the use of antibody-based therapies. Antibodies

targeting Aβ are neuroprotective in rodent models (Busche et al., 2015; Bales et al., 2016; Wisniewski and Goñi, 2015). Preliminary studies suggest that they may be beneficial to humans (Sevigny et al., 2016). Similarly, antibodies directed against tau blocked the pathogenic protein aggregates outside of the cells, in the inter-cellular space (Kfoury et al., 2012; Yanamandra et al., 2013 Pedersen and Sigurdsson, 2015; Castillo-Carranza et al., 2015). Immunization also prevented pathogenic α-syn from interacting with cells (Mandler et al., 2014, 2015; Tran et al., 2014). The precise mechanisms of antibody-mediated clearance of misfolded assemblies are unclear, and it is believed that microglia play a critical role in the clearance of antibody-bound assemblies. Other clearance mechanisms may include blockade of neuronal uptake (Funk et al., 2015) by therapeutic antibodies. Antibodies targeting extracellular pathogenic protein aggregates only recently showed some effectiveness in patients with AD and other neurodegenerative diseases (Ising et al., 2015; Sevigny et al., 2016). The shortcomings of this and other clinical trials is that they were mostly initiated late in the course of the disease, when neurodegenerative symptoms are well established. The development of amyloid imaging methods in AD and novel biomarkers should help to resolve this problem in the future and allow the studies to be carried out earlier. Currently, there are several ongoing pre-clinical and clinical studies validating the therapeutic potential of antibodies targeting Aβ (Ising et al., 2015; Sevigny et al., 2016), tau (Pedersen and Sigurdsson, 2015), and α-syn (Bergström et al., 2016).

Counteracting Pathogenic Protein Assembly-Mediated Membrane Protein Redistribution

The clustering of membrane proteins following the binding of pathogenic assemblies results in a gain of function or loss of function as described above (Figure 3). Strategies relying on identification of the surface interfaces between pathogenic protein assemblies and their membranous partners possess therapeutic potential. The α3-NKA site that interacts with Aβ assemblies was identified based on molecular modeling (Ohnishi et al., 2015). Small peptides reproducing this interface prevented Aβ assemblies from interacting with α3-NKA and were shown to be neuroprotective in a preliminary in vitro study (Ohnishi et al., 2015). Similarly, small peptides preventing Aβ binding to EphB2 rescued the impaired synaptic plasticity and memory deficits in a mouse model of AD by modulating NMDA receptors (Shi et al., 2016). This suggests that the peptides may have acted as a decoy to lure Aβ aggregates away from interacting membrane receptors and emphasizes the therapeutic potential of targeting specific interfaces between pathogenic protein aggregates and their membrane protein partners.

New knowledge about the deleterious interactions between Aβ, α-syn, and tau on one hand and plasma membrane proteins on the other hand will make it possible to develop antibodies with epitopes targeting the interaction domain on plasma membrane proteins. Such protective antibodies have been developed in CJD and proved to be therapeutically efficient in animal studies. The protective antibodies, which bind to the non-structured octapeptide domain of PrP^c, alter their conformations in a way that counteracts the toxicity of misfolded prions (Sonati et al., 2013; Herrmann et al., 2015). In another study, it was shown that antibodies binding to a specific segment on PrP^c decreased their interaction with mGluR5s, a modulator of neurodegeneration in AD (Haas et al., 2014). Thus, immunotherapy targeting membrane partners of pathogenic proteins could offer neuroprotection.

Pharmacological modulation of the plasma membrane proteins that interact with pathogenic proteins is a simpler approach to developing a symptomatic therapy. Several receptors associated with Ca^{2+} signaling have been implicated in the pathophysiology of neurodegenerative disorders, especially AD (Table 1). A causal relationship between Aβ aggregation and mGluR5 dysfunction has also been established, and two different antagonists of mGluR5s reversed memory deficit in AD mouse models (Um et al., 2013; Hamilton et al., 2016). Among other Aβ-interacting membrane proteins, nicotinic acetylcholine receptors agonists/antagonists (Lombardo and Maskos, 2015) and the EphB2 inhibitors (Fu et al., 2014) are promising targets for AD. Several studies have demonstrated hyper-excitability in NMDA receptors in experimental models of AD, and there are clinical trials with moderately inhibitory NMDA receptor antagonists (Howard et al., 2012).

Shielding the membrane target of extracellular Aβ and α-syn is emerging as a novel therapeutic strategy in both AD and PD. Given the number of pathogenic protein assembly partners at the surface of neurons (Table 1), the use of agonists, inhibitors, or inhibitory peptides/antibodies targeting each partner protein may not be a therapeutic strategy that is easy to implement. An alternative strategy may involve the activation of pathogenic protein partners downstream of the signal transduction pathway. Indeed, α-NKA signaling, for instance, results in cell and tissue protection (Aperia et al., 2016). However, this necessitates the development of novel modulators of neuronal pathogenic protein partners that counteract their redistribution upon exposure of neurons to pathogenic protein assemblies involved in AD and PD and compensate for their inactivation following their clustering; for example, by inducing their expression and/or restoring or mimicking their normal function and/or signaling activities. Thus, interfering with pathologic misfolded protein interaction with cell membranes by changing their surface properties in a way so that they are not capable of binding membrane-associated partner proteins and/or shielding their receptors will represent a novel avenue to halt or slow down the progression of AD, PD, and many other neurodegenerative diseases.

Limitations and Future Perspectives

Although cell-to-cell transmission of pathogenic protein assemblies has been demonstrated, the contribution of this process to disease is questioned. This is due to the experimental setups that have been used and due to atypical PD and AD cases, representing up to 15%–20% of the cases that exhibit pathogenic patterns dissimilar from those reported by Braak and coworkers (Braak and Braak, 1991; Braak et al., 2003). Indeed, most of the experimental setups used so far are imperfect. High concentrations of pathogenic assemblies ranging from micromolar to nanomolar have been used to allow detection of the pathogenic assemblies. In addition, to favor amplification, transgenic animals, either overexpressing proteins which aggregation is involved in disease or variants of these proteins associated with familial forms of diseases with early onset, have been

employed in most studies. These limitations can be surpassed by the use and development of highly sensitive, dynamic imaging tools such as structured illumination microscopy (Hong et al., 2016), photo-activated localization microscopy (PALM)/STORM (stochastic optical reconstruction microscopy) imaging (Sigal et al., 2015), tissue clearing (Liebmann et al., 2016), and expansion approaches (Chen et al., 2015). The use of mature neurons with well-developed synapses/spines, human-derived neuronal cells, and new animal models better suited to document human age-related disorders should also be developed. Despite the limitations listed above, the finding that fibrillar assemblies with distinct surfaces and structures yield different pathologies in animal models (Kaufman et al., 2016; Peelaerts et al., 2015) strongly suggests that the interaction of divergent pathogenic assemblies with membranous partners and the redistribution of membrane protein partners they trigger specifically is critical for understanding neurodegenerative diseases progression. This is why it is mandatory to assess, at the highest possible resolution, the consequences of distinct pathogenic protein assembly binding to neuronal cell membranes to better understand the molecular processes leading to disease.

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REFERENCES

Abounit, S., Bousset, L., Loria, F., Zhu, S., de Chaumont, F., Pieri, L., Olivo-Marin, J.-C., Melki, R., and Zurzolo, C. (2016). Tunneling nanotubes spread fibrillar α-synuclein by intercellular trafficking of lysosomes. EMBO J. *35*, 2120–2138.

Aguzzi, A., and Falsig, J. (2012). Prion propagation, toxicity and degradation. Nat. Neurosci. *15*, 936–939.

Akkuratov, E.E., Lopacheva, O.M., Kruusmägi, M., Lopachev, A.V., Shah, Z.A., Boldyrev, A.A., and Liu, L. (2015). Functional Interaction Between Na/K-ATPase and NMDA Receptor in Cerebellar Neurons. Mol. Neurobiol. *52*, 1726–1734.

Antonny, B. (2011). Mechanisms of membrane curvature sensing. Annu. Rev. Biochem. *80*, 101–123.

Anunciado, D., Rai, D.K., Qian, S., Urban, V., and O'Neill, H. (2015). Small-angle neutron scattering reveals the assembly of alpha-synuclein in lipid membranes. Biochim. Biophys. Acta *1854*, 1881–1889.

Aperia, A., Akkuratov, E.E., Fontana, J.M., and Brismar, H. (2016). Na+-K+-ATPase, a new class of plasma membrane receptors. Am. J. Physiol. Cell Physiol. *310*, C491–C495.

Avdulov, N.A., Chochina, S.V., Igbavboa, U., Warden, C.S., Vassiliev, A.V., and Wood, W.G. (1997). Lipid binding to amyloid beta-peptide aggregates: preferential binding of cholesterol as compared with phosphatidylcholine and fatty acids. J. Neurochem. *69*, 1746–1752.

Azarias, G., Kruusmägi, M., Connor, S., Akkuratov, E.E., Liu, X.-L., Lyons, D., Brismar, H., Broberger, C., and Aperia, A. (2013). A specific and essential role for Na,K-ATPase α3 in neurons co-expressing α1 and α3. J. Biol. Chem. *288*, 2734–2743.

Balducci, C., Beeg, M., Stravalaci, M., Bastone, A., Sclip, A., Biasini, E., Tapella, L., Colombo, L., Manzoni, C., Borsello, T., et al. (2010). Synthetic amyloid-beta oligomers impair long-term memory independently of cellular prion protein. Proc. Natl. Acad. Sci. USA *107*, 2295–2300.

Bales, K.R., O'Neill, S.M., Pozdnyakov, N., Pan, F., Caouette, D., Pi, Y., Wood, K.M., Volfson, D., Cirrito, J.R., Han, B.-H., et al. (2016). Passive immunotherapy targeting amyloid-β reduces cerebral amyloid angiopathy and improves vascular reactivity. Brain *139*, 563–577.

Bellani, S., Mescola, A., Ronzitti, G., Tsushima, H., Tilve, S., Canale, C., Valtorta, F., and Chieregatti, E. (2014). GRP78 clustering at the cell surface of neurons transduces the action of exogenous alpha-synuclein. Cell Death Differ. *21*, 1971–1983.

Ben-Naim, E., Krapivsky, P.L., and Redner, S. (2008). Fundamental kinetic processes (Boston University).

Benskey, M.J., Perez, R.G., and Manfredsson, F.P. (2016). The contribution of alpha synuclein to neuronal survival and function - Implications for Parkinson's disease. J. Neurochem. *137*, 331–359.

Bergström, A.L., Kallunki, P., and Fog, K. (2016). Development of Passive Immunotherapies for Synucleinopathies. Mov. Disord. *31*, 203–213.

Bokvist, M., and Gröbner, G. (2007). Misfolding of amyloidogenic proteins at membrane surfaces: the impact of macromolecular crowding. J. Am. Chem. Soc. *129*, 14848–14849.

Bokvist, M., Lindström, F., Watts, A., and Gröbner, G. (2004). Two types of Alzheimer's β-amyloid (1-40) peptide membrane interactions: aggregation preventing transmembrane anchoring versus accelerated surface fibril formation. J. Mol. Biol. *335*, 1039–1049.

Bosch-Morató, M., Iriondo, C., Guivernau, B., Valls-Comamala, V., Vidal, N., Olivé, M., Querfurth, H., and Muñoz, F.J. (2016). Increased amyloid β-peptide uptake in skeletal muscle is induced by hyposialylation and may account for apoptosis in GNE myopathy. Oncotarget *7*, 13354–13371.

Bouchaud, J.P., and Georges, A. (1990). Anomalous diffusion in disordered media - statistical mechanisms, models and physical applications. Phys. Rep. Rev. Sec. Phys. Lett. *195*, 127–293.

Bousset, L., Pieri, L., Ruiz-Arlandis, G., Gath, J., Jensen, P.H., Habenstein, B., Madiona, K., Olieric, V., Böckmann, A., Meier, B.H., and Melki, R. (2013). Structural and functional characterization of two alpha-synuclein strains. Nat. Commun. *4*, 2575.

Braak, H., and Braak, E. (1991). Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol. *82*, 239–259.

Braak, H., Del Tredici, K., Rüb, U., de Vos, R.A., Jansen Steur, E.N., and Braak, E. (2003). Staging of brain pathology related to sporadic Parkinson's disease. Neurobiol Aging. *24*, 197–211.

Brahic, M., Bousset, L., Bieri, G., Melki, R., and Gitler, A.D. (2016). Axonal transport and secretion of fibrillar forms of α-synuclein, Aβ42 peptide and HTTExon 1. Acta Neuropathol. *131*, 539–548.

Brandner, S., Isenmann, S., Raeber, A., Fischer, M., Sailer, A., Kobayashi, Y., Marino, S., Weissmann, C., and Aguzzi, A. (1996). Normal host prion protein necessary for scrapie-induced neurotoxicity. Nature *379*, 339–343.

Brito-Moreira, J., Lourenco, M.V., Oliveira, M.M., Ribeiro, F.C., Ledo, J.H., Diniz, L.P., Vital, J.F.S., Magdesian, M.H., Melo, H.M., Barros-Aragão, F., et al. (2017). Interaction of amyloid-β (Aβ) oligomers with neurexin 2α and neuroligin 1 mediates synapse damage and memory loss in mice. J. Biol. Chem. *292*, 7327–7337.

Brückner, G., Hausen, D., Härtig, W., Drlicek, M., Arendt, T., and Brauer, K. (1999). Cortical areas abundant in extracellular matrix chondroitin sulphate proteoglycans are less affected by cytoskeletal changes in Alzheimer's disease. Neuroscience *92*, 791–805.

Brundin, P., Melki, R., and Kopito, R. (2010). Prion-like transmission of protein aggregates in neurodegenerative diseases. Nat. Rev. Mol. Cell Biol. *11*, 301–307.

Burke, K.A., Hensal, K.M., Umbaugh, C.S., Chaibva, M., and Legleiter, J. (2013). Huntingtin disrupts lipid bilayers in a polyQ-length dependent manner. Biochim. Biophys. Acta *1828*, 1953–1961.

Busche, M.A., Grienberger, C., Keskin, A.D., Song, B., Neumann, U., Staufenbiel, M., Förstl, H., and Konnerth, A. (2015). Decreased amyloid-β and increased neuronal hyperactivity by immunotherapy in Alzheimer's models. Nat. Neurosci. *18*, 1725–1727.

Byström, R., Aisenbrey, C., Borowik, T., Bokvist, M., Lindström, F., Sani, M.A., Olofsson, A., and Gröbner, G. (2008). Disordered proteins: biological membranes as two-dimensional aggregation matrices. Cell Biochem. Biophys. *52*, 175–189.

Calamai, M., and Pavone, F.S. (2013). Partitioning and confinement of GM1 ganglioside induced by amyloid aggregates. FEBS Lett. *587*, 1385–1391.

Calamai, M., Evangelisti, E., Cascella, R., Parenti, N., Cecchi, C., Stefani, M., and Pavone, F. (2016). Single molecule experiments emphasize GM1 as a key player of the different cytotoxicity of structurally distinct Aβ1-42 oligomers. Biochim. Biophys. Acta *1858*, 386–392.

Calella, A.M., Farinelli, M., Nuvolone, M., Mirante, O., Moos, R., Falsig, J., Mansuy, I.M., and Aguzzi, A. (2010). Prion protein and Abeta-related synaptic toxicity impairment. EMBO Mol. Med. *2*, 306–314.

Casley, C.S., Lakics, V., Lee, H.-G., Broad, L.M., Day, T.A., Cluett, T., Smith, M.A., O'Neill, M.J., and Kingston, A.E. (2009). Up-regulation of astrocyte metabotropic glutamate receptor 5 by amyloid-β peptide. Brain Res. *1260*, 65–75.

Castillo, G.M., Ngo, C., Cummings, J., Wight, T.N., and Snow, A.D. (1997). Perlecan binds to the beta-amyloid proteins (A beta) of Alzheimer's disease, accelerates A beta fibril formation, and maintains A beta fibril stability. J. Neurochem. *69*, 2452–2465.

Castillo-Carranza, D.L., Guerrero-Muñoz, M.J., Sengupta, U., Hernandez, C., Barrett, A.D.T., Dineley, K., and Kayed, R. (2015). Tau immunotherapy modulates both pathological tau and upstream amyloid pathology in an Alzheimer's disease mouse model. J. Neurosci. *35*, 4857–4868.

Caughey, B., Brown, K., Raymond, G.J., Katzenstein, G.E., and Thresher, W. (1994). Binding of the protease-sensitive form of PrP (prion protein) to sulfated glycosaminoglycan and congo red [corrected]. J. Virol. *68*, 2135–2141.

Chamma, I., Letellier, M., Butler, C., Tessier, B., Lim, K.H., Gauthereau, I., Choquet, D., Sibarita, J.B., Park, S., Sainlos, M., and Thoumine, O. (2016). Mapping the dynamics and nanoscale organization of synaptic adhesion proteins using monomeric streptavidin. Nat. Commun. *7*, 10773.

Chasseigneaux, S., and Allinquant, B. (2012). Functions of Aβ, sAPPα and sAPPβ : similarities and differences. J. Neurochem. *120* (*Suppl 1*), 99–108.

Chen, F., Tillberg, P.W., and Boyden, E.S. (2015). Optical imaging. Expansion microscopy. Science *347*, 543–548.

Choquet, D., and Triller, A. (2013). The dynamic synapse. Neuron *80*, 691–703.

Cissé, M., Halabisky, B., Harris, J., Devidze, N., Dubal, D.B., Sun, B., Orr, A., Lotz, G., Kim, D.H., Hamto, P., et al. (2011a). Reversing EphB2 depletion rescues cognitive functions in Alzheimer model. Nature *469*, 47–52.

Cissé, M., Sanchez, P.E., Kim, D.H., Ho, K., Yu, G.-Q., and Mucke, L. (2011b). Ablation of cellular prion protein does not ameliorate abnormal neural network activity or cognitive dysfunction in the J20 line of human amyloid precursor protein transgenic mice. J. Neurosci. *31*, 10427–10431.

Cohlberg, J.A., Li, J., Uversky, V.N., and Fink, A.L. (2002). Heparin and other glycosaminoglycans stimulate the formation of amyloid fibrils from alpha-synuclein in vitro. Biochemistry *41*, 1502–1511.

Collinge, J., and Clarke, A.R. (2007). A general model of prion strains and their pathogenicity. Science *318*, 930–936.

Cotman, S.L., Halfter, W., and Cole, G.J. (2000). Agrin binds to beta-amyloid (Abeta), accelerates abeta fibril formation, and is localized to Abeta deposits in Alzheimer's disease brain. Mol. Cell. Neurosci. *15*, 183–198.

Cremades, N., Cohen, S.I.A., Deas, E., Abramov, A.Y., Chen, A.Y., Orte, A., Sandal, M., Clarke, R.W., Dunne, P., Aprile, F.A., et al. (2012). Direct observation of the interconversion of normal and toxic forms of α-synuclein. Cell *149*, 1048–1059.

Danzer, K.M., Haasen, D., Karow, A.R., Moussaud, S., Habeck, M., Giese, A., Kretzschmar, H., Hengerer, B., and Kostka, M. (2007). Different species of alpha-synuclein oligomers induce calcium influx and seeding. J. Neurosci. *27*, 9220–9232.

De Felice, F.G., Velasco, P.T., Lambert, M.P., Viola, K., Fernandez, S.J., Ferreira, S.T., and Klein, W.L. (2007). Abeta oligomers induce neuronal oxidative stress through an N-methyl-D-aspartate receptor-dependent mechanism that is blocked by the Alzheimer drug memantine. J. Biol. Chem. *282*, 11590–11601.

Di Pasquale, E., Fantini, J., Chahinian, H., Maresca, M., Taïeb, N., and Yahi, N. (2010). Altered ion channel formation by the Parkinson's-disease-linked E46K mutant of alpha-synuclein is corrected by GM3 but not by GM1 gangliosides. J. Mol. Biol. *397*, 202–218.

Di Scala, C., Chahinian, H., Yahi, N., Garmy, N., and Fantini, J. (2014). Interaction of Alzheimer's β-amyloid peptides with cholesterol: mechanistic insights into amyloid pore formation. Biochemistry *53*, 4489–4502.

Dinamarca, M.C., Weinstein, D., Monasterio, O., and Inestrosa, N.C. (2011). The synaptic protein neuroligin-1 interacts with the amyloid β-peptide. Is there a role in Alzheimer's disease? Biochemistry *50*, 8127–8137.

Dineley, K.T., Westerman, M., Bui, D., Bell, K., Ashe, K.H., and Sweatt, J.D. (2001). Beta-amyloid activates the mitogen-activated protein kinase cascade via hippocampal alpha7 nicotinic acetylcholine receptors: In vitro and in vivo mechanisms related to Alzheimer's disease. J. Neurosci. *21*, 4125–4133.

Diógenes, M.J., Dias, R.B., Rombo, D.M., Vicente Miranda, H., Maiolino, F., Guerreiro, P., Näsström, T., Franquelim, H.G., Oliveira, L.M.A., Castanho, M.A.R.B., et al. (2012). Extracellular alpha-synuclein oligomers modulate synaptic transmission and impair LTP via NMDA-receptor activation. J. Neurosci. *32*, 11750–11762.

Dix, J.A., and Verkman, A.S. (2008). Crowding effects on diffusion in solutions and cells. Annu. Rev. Biophys. *37*, 247–263.

Dziewczapolski, G., Glogowski, C.M., Masliah, E., and Heinemann, S.F. (2009). Deletion of the alpha 7 nicotinic acetylcholine receptor gene improves cognitive deficits and synaptic pathology in a mouse model of Alzheimer's disease. J. Neurosci. *29*, 8805–8815.

Eggeling, C., Ringemann, C., Medda, R., Schwarzmann, G., Sandhoff, K., Polyakova, S., Belov, V.N., Hein, B., von Middendorff, C., Schönle, A., and Hell, S.W. (2009). Direct observation of the nanoscale dynamics of membrane lipids in a living cell. Nature *457*, 1159–1162.

Ehrnhoefer, D.E., Bieschke, J., Boeddrich, A., Herbst, M., Masino, L., Lurz, R., Engemann, S., Pastore, A., and Wanker, E.E. (2008). EGCG redirects amyloidogenic polypeptides into unstructured, off-pathway oligomers. Nat. Struct. Mol. Biol. *15*, 558–566.

Einstein, A. (1905). Über die von der molekularkinetischen theorie der wärme gefordete bewegung von in ruhenden flüssigkeiten suspendierten teilchen. Ann. Phys. *322*, 549–560.

Eisenberg, D., and Jucker, M. (2012). The amyloid state of proteins in human diseases. Cell *148*, 1188–1203.

Fantini, J., and Yahi, N. (2011). Molecular basis for the glycosphingolipid-binding specificity of α-synuclein: key role of tyrosine 39 in membrane insertion. J. Mol. Biol. *408*, 654–669.

Fantini, J., and Yahi, N. (2013). The driving force of alpha-synuclein insertion and amyloid channel formation in the plasma membrane of neural cells: key role of ganglioside- and cholesterol-binding domains. Adv. Exp. Med. Biol. *991*, 15–26.

Fantini, J., Carlus, D., and Yahi, N. (2011). The fusogenic tilted peptide (67-78) of α-synuclein is a cholesterol binding domain. Biochim. Biophys. Acta *1808*, 2343–2351.

Fersht, A.R. (1999). Structure and Mechanism in Protein Science: A Guide to Enzyme Catalysis and Protein Folding (W. H. Freeman).

Fraser, P.E., Nguyen, J.T., Chin, D.T., and Kirschner, D.A. (1992). Effects of sulfate ions on Alzheimer beta/A4 peptide assemblies: implications for amyloid fibril-proteoglycan interactions. J. Neurochem. *59*, 1531–1540.

Fu, W., Ruangkittisakul, A., MacTavish, D., Shi, J.Y., Ballanyi, K., and Jhamandas, J.H. (2012). Amyloid β (Aβ) peptide directly activates amylin-3 receptor subtype by triggering multiple intracellular signaling pathways. J. Biol. Chem. *287*, 18820–18830.

Fu, A.K.Y., Hung, K.-W., Huang, H., Gu, S., Shen, Y., Cheng, E.Y.L., Ip, F.C.F., Huang, X., Fu, W.-Y., and Ip, N.Y. (2014). Blockade of EphA4 signaling ameliorates hippocampal synaptic dysfunctions in mouse models of Alzheimer's disease. Proc. Natl. Acad. Sci. USA *111*, 9959–9964.

Funk, K.E., Mirbaha, H., Jiang, H., Holtzman, D.M., and Diamond, M.I. (2015). Distinct therapeutic mechanisms of tau antibodies: promoting microglial clearance versus blocking neuronal uptake. J. Biol. Chem. *290*, 21652–21662.

Ganzinger, K.A., Narayan, P., Qamar, S.S., Weimann, L., Ranasinghe, R.T., Aguzzi, A., Dobson, C.M., McColl, J., St George-Hyslop, P., and Klenerman, D. (2014). Single-molecule imaging reveals that small amyloid-β1-42 oligomers interact with the cellular prion protein (PrP(C)). ChemBioChem *15*, 2515–2521.

Garten, M., Prévost, C., Cadart, C., Gautier, R., Bousset, L., Melki, R., Bassereau, P., and Vanni, S. (2015). Methyl-branched lipids promote the membrane adsorption of α-synuclein by enhancing shallow lipid-packing defects. Phys. Chem. Chem. Phys. *17*, 15589–15597.

Godsave, S.F., Wille, H., Pierson, J., Prusiner, S.B., and Peters, P.J. (2013). Plasma membrane invaginations containing clusters of full-length PrPSc are an early form of prion-associated neuropathology in vivo. Neurobiol. Aging *34*, 1621–1631.

Goedert, M. (2015). Alzheimer's and Parkinson's diseases: The prion concept in relation to assembled Aβ, tau, and α-synuclein. Science *349*, 1255555.

Goedert, M., Jakes, R., Spillantini, M.G., Hasegawa, M., Smith, M.J., and Crowther, R.A. (1996). Assembly of microtubule-associated protein tau into Alzheimer-like filaments induced by sulphated glycosaminoglycans. Nature *383*, 550–553.

Goedert, M., Clavaguera, F., and Tolnay, M. (2010). The propagation of prion-like protein inclusions in neurodegenerative diseases. Trends Neurosci. *33*, 317–325.

Goldberg, M.S., and Lansbury, P.T., Jr. (2000). Is there a cause-and-effect relationship between alpha-synuclein fibrillization and Parkinson's disease? Nat. Cell Biol. *2*, E115–E119.

Gómez-Ramos, A., Díaz-Hernández, M., Rubio, A., Miras-Portugal, M.T., and Avila, J. (2008). Extracellular tau promotes intracellular calcium increase through M1 and M3 muscarinic receptors in neuronal cells. Mol. Cell. Neurosci. *37*, 673–681.

Goold, R., Rabbanian, S., Sutton, L., Andre, R., Arora, P., Moonga, J., Clarke, A.R., Schiavo, G., Jat, P., Collinge, J., and Tabrizi, S.J. (2011). Rapid cell-surface prion protein conversion revealed using a novel cell system. Nat. Commun. *2*, 281.

Haas, L.T., Kostylev, M.A., and Strittmatter, S.M. (2014). Therapeutic molecules and endogenous ligands regulate the interaction between brain cellular prion protein (PrPC) and metabotropic glutamate receptor 5 (mGluR5). J. Biol. Chem. *289*, 28460–28477.

Haas, L.T., Salazar, S.V., Kostylev, M.A., Um, J.W., Kaufman, A.C., and Strittmatter, S.M. (2016). Metabotropic glutamate receptor 5 couples cellular prion protein to intracellular signalling in Alzheimer's disease. Brain *139*, 526–546.

Hamilton, A., Esseltine, J.L., DeVries, R.A., Cregan, S.P., and Ferguson, S.S.G. (2014). Metabotropic glutamate receptor 5 knockout reduces cognitive impairment and pathogenesis in a mouse model of Alzheimer's disease. Mol. Brain *7*, 40.

Hamilton, A., Vasefi, M., Vander Tuin, C., McQuaid, R.J., Anisman, H., and Ferguson, S.S.G. (2016). Chronic pharmacological mglur5 inhibition prevents cognitive impairment and reduces pathogenesis in an Alzheimer disease mouse model. Cell Rep. *15*, 1859–1865.

Hansen, C., Angot, E., Bergström, A.-L., Steiner, J.A., Pieri, L., Paul, G., Outeiro, T.F., Melki, R., Kallunki, P., Fog, K., et al. (2011). α-Synuclein propagates from mouse brain to grafted dopaminergic neurons and seeds aggregation in cultured human cells. J. Clin. Invest. *121*, 715–725.

Harris, J.J., Jolivet, R., and Attwell, D. (2012). Synaptic energy use and supply. Neuron *75*, 762–777.

Härtig, W., Klein, C., Brauer, K., Schüppel, K.F., Arendt, T., Bigl, V., and Brückner, G. (2001). Hyperphosphorylated protein tau is restricted to neurons devoid of perineuronal nets in the cortex of aged bison. Neurobiol. Aging *22*, 25–33.

Heinzen, E.L., Arzimanoglou, A., Brashear, A., Clapcote, S.J., Gurrieri, F., Goldstein, D.B., Jóhannesson, S.H., Mikati, M.A., Neville, B., Nicole, S., et al.; ATP1A3 Working Group (2014). Distinct neurological disorders with ATP1A3 mutations. Lancet Neurol. *13*, 503–514.

Hellstrand, E., Nowacka, A., Topgaard, D., Linse, S., and Sparr, E. (2013). Membrane lipid co-aggregation with α-synuclein fibrils. PLoS ONE *8*, e77235.

Herrmann, U.S., Sonati, T., Falsig, J., Reimann, R.R., Dametto, P., O'Connor, T., Li, B., Lau, A., Hornemann, S., Sorce, S., et al. (2015). Prion infections and anti-PrP antibodies trigger converging neurotoxic pathways. PLoS Pathog. *11*, e1004662.

Holmes, B.B., DeVos, S.L., Kfoury, N., Li, M., Jacks, R., Yanamandra, K., Ouidja, M.O., Brodsky, F.M., Marasa, J., Bagchi, D.P., et al. (2013). Heparan sulfate proteoglycans mediate internalization and propagation of specific proteopathic seeds. Proc. Natl. Acad. Sci. USA *110*, E3138–E3147.

Hong, S., Ostaszewski, B.L., Yang, T., O'Malley, T.T., Jin, M., Yanagisawa, K., Li, S., Bartels, T., and Selkoe, D.J. (2014). Soluble Aβ oligomers are rapidly sequestered from brain ISF in vivo and bind GM1 ganglioside on cellular membranes. Neuron *82*, 308–319.

Hong, S., Beja-Glasser, V.F., Nfonoyim, B.M., Frouin, A., Li, S., Ramakrishnan, S., Merry, K.M., Shi, Q., Rosenthal, A., Barres, B.A., et al. (2016). Complement and microglia mediate early synapse loss in Alzheimer mouse models. Science *352*, 712–716.

Horonchik, L., Tzaban, S., Ben-Zaken, O., Yedidia, Y., Rouvinski, A., Papy-Garcia, D., Barritault, D., Vlodavsky, I., and Taraboulos, A. (2005). Heparan sulfate is a cellular receptor for purified infectious prions. J. Biol. Chem. *280*, 17062–17067.

Howard, R., McShane, R., Lindesay, J., Ritchie, C., Baldwin, A., Barber, R., Burns, A., Dening, T., Findlay, D., Holmes, C., et al. (2012). Donepezil and memantine for moderate-to-severe Alzheimer's disease. N. Engl. J. Med. *366*, 893–903.

Hu, N.W., Nicoll, A.J., Zhang, D., Mably, A.J., O'Malley, T., Purro, S.A., Terry, C., Collinge, J., Walsh, D.M., and Rowan, M.J. (2014). mGlu5 receptors and cellular prion protein mediate amyloid-β-facilitated synaptic long-term depression in vivo. Nat. Commun. *5*, 3374.

Ising, C., Stanley, M., and Holtzman, D.M. (2015). Current thinking on the mechanistic basis of Alzheimer's and implications for drug development. Clin. Pharmacol. Ther. *98*, 469–471.

Izzo, N.J., Xu, J., Zeng, C., Kirk, M.J., Mozzoni, K., Silky, C., Rehak, C., Yurko, R., Look, G., Rishton, G., et al. (2014). Alzheimer's therapeutics targeting amyloid beta 1-42 oligomers II: Sigma-2/PGRMC1 receptors mediate Abeta 42 oligomer binding and synaptotoxicity. PLoS ONE *9*, e111899.

Jarosz-Griffiths, H.H., Noble, E., Rushworth, J.V., and Hooper, N.M. (2016). Amyloid-β receptors: the good, the bad, and the prion protein. J. Biol. Chem. *291*, 3174–3183.

Johri, A., and Beal, M.F. (2012). Mitochondrial dysfunction in neurodegenerative diseases. J. Pharmacol. Exp. Ther. *342*, 619–630.

Jones, E.M., Dubey, M., Camp, P.J., Vernon, B.C., Biernat, J., Mandelkow, E., Majewski, J., and Chi, E.Y. (2012). Interaction of tau protein with model lipid membranes induces tau structural compaction and membrane disruption. Biochemistry *51*, 2539–2550.

Jucker, M., and Walker, L.C. (2013). Self-propagation of pathogenic protein aggregates in neurodegenerative diseases. Nature *501*, 45–51.

Kam, T.-I., Song, S., Gwon, Y., Park, H., Yan, J.-J., Im, I., Choi, J.-W., Choi, T.-Y., Kim, J., Song, D.-K., et al. (2013). FcγRIIb mediates amyloid-β

neurotoxicity and memory impairment in Alzheimer's disease. J. Clin. Invest. *123*, 2791–2802.

Kanekiyo, T., Zhang, J., Liu, Q., Liu, C.-C., Zhang, L., and Bu, G. (2011). Heparan sulphate proteoglycan and the low-density lipoprotein receptor-related protein 1 constitute major pathways for neuronal amyloid-beta uptake. J. Neurosci. *31*, 1644–1651.

Kaplan, J.H. (2002). Biochemistry of Na,K-ATPase. Annu Rev Biochem. *71*, 511–535.

Kaufman, S.K., Sanders, D.W., Thomas, T.L., Ruchinskas, A.J., Vaquer-Alicea, J., Sharma, A.M., Miller, T.M., and Diamond, M.I. (2016). Tau prion strains dictate patterns of cell pathology, progression rate, and regional vulnerability in vivo. Neuron *92*, 796–812.

Kayed, R., Head, E., Thompson, J.L., McIntire, T.M., Milton, S.C., Cotman, C.W., and Glabe, C.G. (2003). Common structure of soluble amyloid oligomers implies common mechanism of pathogenesis. Science *300*, 486–489.

Kayed, R., Sokolov, Y., Edmonds, B., McIntire, T.M., Milton, S.C., Hall, J.E., and Glabe, C.G. (2004). Permeabilization of lipid bilayers is a common conformation-dependent activity of soluble amyloid oligomers in protein misfolding diseases. J. Biol. Chem. *279*, 46363–46366.

Kessels, H.W., Nguyen, L.N., Nabavi, S., and Malinow, R. (2010). The prion protein as a receptor for amyloid-beta. Nature *466*, E3–E4, discussion E4–E5.

Kfoury, N., Holmes, B.B., Jiang, H., Holtzman, D.M., and Diamond, M.I. (2012). Trans-cellular propagation of Tau aggregation by fibrillar species. J. Biol. Chem. *287*, 19440–19451.

Kim, T., Vidal, G.S., Djurisic, M., William, C.M., Birnbaum, M.E., Garcia, K.C., Hyman, B.T., and Shatz, C.J. (2013). Human LilrB2 is a β-amyloid receptor and its murine homolog PirB regulates synaptic plasticity in an Alzheimer's model. Science *341*, 1399–1404.

Knafo, S., Sánchez-Puelles, C., Palomer, E., Delgado, I., Draffin, J.E., Mingo, J., Wahle, T., Kaleka, K., Mou, L., Pereda-Perez, I., et al. (2016). PTEN recruitment controls synaptic and cognitive function in Alzheimer's models. Nat. Neurosci. *19*, 443–453.

Kokubo, H., Saido, T.C., Iwata, N., Helms, J.B., Shinohara, R., and Yamaguchi, H. (2005). Part of membrane-bound Abeta exists in rafts within senile plaques in Tg2576 mouse brain. Neurobiol. Aging *26*, 409–418.

Kostka, M., Högen, T., Danzer, K.M., Levin, J., Habeck, M., Wirth, A., Wagner, R., Glabe, C.G., Finger, S., Heinzelmann, U., et al. (2008). Single particle characterization of iron-induced pore-forming alpha-synuclein oligomers. J. Biol. Chem. *283*, 10992–11003.

Küffer, A., Lakkaraju, A.K.K., Mogha, A., Petersen, S.C., Airich, K., Doucerain, C., Marpakwar, R., Bakirci, P., Senatore, A., Monnard, A., et al. (2016). The prion protein is an agonistic ligand of the G protein-coupled receptor Adgrg6. Nature *536*, 464–468.

Lashuel, H.A., Petre, B.M., Wall, J., Simon, M., Nowak, R.J., Walz, T., and Lansbury, P.T., Jr. (2002). Alpha-synuclein, especially the Parkinson's disease-associated mutants, forms pore-like annular and tubular protofibrils. J. Mol. Biol. *322*, 1089–1102.

Laurén, J., Gimbel, D.A., Nygaard, H.B., Gilbert, J.W., and Strittmatter, S.M. (2009). Cellular prion protein mediates impairment of synaptic plasticity by amyloid-beta oligomers. Nature *457*, 1128–1132.

Li, H., and Gorfe, A.A. (2014). Membrane remodeling by surface-bound protein aggregates: insights from coarse-grained molecular dynamics simulation. J. Phys. Chem. Lett. *5*, 1457–1462.

Li, S., Jin, M., Koeglsperger, T., Shepardson, N.E., Shankar, G.M., and Selkoe, D.J. (2011). Soluble Aβ oligomers inhibit long-term potentiation through a mechanism involving excessive activation of extrasynaptic NR2B-containing NMDA receptors. J. Neurosci. *31*, 6627–6638.

Li, L., Liu, H., Dong, P., Li, D., Legant, W.R., Grimm, J.B., Lavis, L.D., Betzig, E., Tjian, R., and Liu, Z. (2016). Real-time imaging of Huntingtin aggregates diverting target search and gene transcription. eLife *5*, e17056.

Liebmann, T., Renier, N., Bettayeb, K., Greengard, P., Tessier-Lavigne, M., and Flajolet, M. (2016). Three-dimensional study of Alzheimer's disease hallmarks using the iDISCO clearing method. Cell Rep. *16*, 1138–1152.

Lim, D., Iyer, A., Ronco, V., Grolla, A.A., Canonico, P.L., Aronica, E., and Genazzani, A.A. (2013). Amyloid beta deregulates astroglial mGluR5-mediated calcium signaling via calcineurin and Nf-kB. Glia *61*, 1134–1145.

Liu, I.H., Uversky, V.N., Munishkina, L.A., Fink, A.L., Halfter, W., and Cole, G.J. (2005). Agrin binds alpha-synuclein and modulates alpha-synuclein fibrillation. Glycobiology *15*, 1320–1331.

Lombardo, S., and Maskos, U. (2015). Role of the nicotinic acetylcholine receptor in Alzheimer's disease pathology and treatment. Neuropharmacology *96* (Pt B), 255–262.

Magdesian, M.H., Carvalho, M.M.V.F., Mendes, F.A., Saraiva, L.M., Juliano, M.A., Juliano, L., Garcia-Abreu, J., and Ferreira, S.T. (2008). Amyloid-beta binds to the extracellular cysteine-rich domain of Frizzled and inhibits Wnt/beta-catenin signaling. J. Biol. Chem. *283*, 9359–9368.

Mahul-Mellier, A.-L., Vercruysse, F., Maco, B., Ait-Bouziad, N., De Roo, M., Muller, D., and Lashuel, H.A. (2015). Fibril growth and seeding capacity play key roles in α-synuclein-mediated apoptotic cell death. Cell Death Differ. *22*, 2107–2122.

Mandler, M., Valera, E., Rockenstein, E., Weninger, H., Patrick, C., Adame, A., Santic, R., Meindl, S., Vigl, B., Smrzka, O., et al. (2014). Next-generation active immunization approach for synucleinopathies: implications for Parkinson's disease clinical trials. Acta Neuropathol. *127*, 861–879.

Mandler, M., Valera, E., Rockenstein, E., Mante, M., Weninger, H., Patrick, C., Adame, A., Schmidhuber, S., Santic, R., Schneeberger, A., et al. (2015). Active immunization against alpha-synuclein ameliorates the degenerative pathology and prevents demyelination in a model of multiple system atrophy. Mol. Neurodegener. *10*, 10.

Mao, X., Ou, M.T., Karuppagounder, S.S., Kam, T.-I., Yin, X., Xiong, Y., Ge, P., Umanah, G.E., Brahmachari, S., Shin, J.-H., et al. (2016). Pathological α-synuclein transmission initiated by binding lymphocyte-activation gene 3. Science *353*, aah3374.

Martinez, Z., Zhu, M., Han, S., and Fink, A.L. (2007). GM1 specifically interacts with alpha-synuclein and inhibits fibrillation. Biochemistry *46*, 1868–1877.

Mattson, M.P. (2007). Calcium and neurodegeneration. Aging Cell *6*, 337–350.

Melki, R. (2015). Role of different alpha-synuclein strains in synucleinopathies, similarities with other neurodegenerative diseases. J. Parkinsons Dis. *5*, 217–227.

Milanesi, L., Sheynis, T., Xue, W.-F., Orlova, E.V., Hellewell, A.L., Jelinek, R., Hewitt, E.W., Radford, S.E., and Saibil, H.R. (2012). Direct three-dimensional visualization of membrane disruption by amyloid fibrils. Proc. Natl. Acad. Sci. USA *109*, 20455–20460.

Miyata, S., Nishimura, Y., and Nakashima, T. (2007). Perineuronal nets protect against amyloid beta-protein neurotoxicity in cultured cortical neurons. Brain Res. *1150*, 200–206.

Molander-Melin, M., Blennow, K., Bogdanovic, N., Dellheden, B., Månsson, J.-E., and Fredman, P. (2005). Structural membrane alterations in Alzheimer brains found to be associated with regional disease development; increased density of gangliosides GM1 and GM2 and loss of cholesterol in detergent-resistant membrane domains. J. Neurochem. *92*, 171–182.

Morawski, M., Brückner, G., Jäger, C., Seeger, G., and Arendt, T. (2010). Neurons associated with aggrecan-based perineuronal nets are protected against tau pathology in subcortical regions in Alzheimer's disease. Neuroscience *169*, 1347–1363.

Morin, N., Morissette, M., Grégoire, L., Gomez-Mancilla, B., Gasparini, F., and Di Paolo, T. (2013). Chronic treatment with MPEP, an mGlu5 receptor antagonist, normalizes basal ganglia glutamate neurotransmission in L-DOPA-treated parkinsonian monkeys. Neuropharmacology *73*, 216–231.

Nagarathinam, A., Höflinger, P., Bühler, A., Schäfer, C., McGovern, G., Jeffrey, M., Staufenbiel, M., Jucker, M., and Baumann, F. (2013). Membrane-anchored

Aβ accelerates amyloid formation and exacerbates amyloid-associated toxicity in mice. J. Neurosci. *33*, 19284–19294.

Naito, Y., Tanabe, Y., Lee, A.K., Hamel, E., and Takahashi, H. (2017). Amyloid-β oligomers interact with neurexin and diminish neurexin-mediated excitatory presynaptic organization. Sci. Rep. *7*, 42548.

Nolt, M.J., Lin, Y., Hruska, M., Murphy, J., Sheffler-Colins, S.I., Kayser, M.S., Passer, J., Bennett, M.V.L., Zukin, R.S., and Dalva, M.B. (2011). EphB controls NMDA receptor function and synaptic targeting in a subunit-specific manner. J. Neurosci. *31*, 5353–5364.

Ohnishi, T., Yanazawa, M., Sasahara, T., Kitamura, Y., Hiroaki, H., Fukazawa, Y., Kii, I., Nishiyama, T., Kakita, A., Takeda, H., et al. (2015). Na, K-ATPase α3 is a death target of Alzheimer patient amyloid-β assembly. Proc. Natl. Acad. Sci. USA *112*, E4465–E4474.

Onuchic, J.N., Socci, N.D., Luthey-Schulten, Z., and Wolynes, P.G. (1996). Protein folding funnels: the nature of the transition state ensemble. Fold. Des. *1*, 441–450.

Oosawa, F., and Asakura, S. (1975). Thermodynamics of the polymerization of proteins, B. Horecker, N.O. Kaplan, R.J. Matmu, and H.A. Scheraga, eds. (London: Academic Press, Inc.).

Overk, C.R., Cartier, A., Shaked, G., Rockenstein, E., Ubhi, K., Spencer, B., Price, D.L., Patrick, C., Desplats, P., and Masliah, E. (2014). Hippocampal neuronal cells that accumulate α-synuclein fragments are more vulnerable to Aβ oligomer toxicity via mGluR5–implications for dementia with Lewy bodies. Mol. Neurodegener. *9*, 18.

Pandey, A.P., Haque, F., Rochet, J.-C., and Hovis, J.S. (2009). Clustering of alpha-synuclein on supported lipid bilayers: role of anionic lipid, protein, and divalent ion concentration. Biophys. J. *96*, 540–551.

Pascual, O., Ben Achour, S., Rostaing, P., Triller, A., and Bessis, A. (2012). Microglia activation triggers astrocyte-mediated modulation of excitatory neurotransmission. Proc. Natl. Acad. Sci. USA *109*, E197–E205.

Patel, N., Ramachandran, S., Azimov, R., Kagan, B.L., and Lal, R. (2015). Ion channel formation by tau protein: implications for Alzheimer's disease and tauopathies. Biochemistry *54*, 7320–7325.

Pearce, M.M., Spartz, E.J., Hong, W., Luo, L., and Kopito, R.R. (2015). Prion-like transmission of neuronal huntingtin aggregates to phagocytic glia in the Drosophila brain. Nat. Commun. *6*, 6768.

Pedersen, J.T., and Sigurdsson, E.M. (2015). Tau immunotherapy for Alzheimer's disease. Trends Mol. Med. *21*, 394–402.

Peelaerts, W., Bousset, L., Van der Perren, A., Moskalyuk, A., Pulizzi, R., Giugliano, M., Van den Haute, C., Melki, R., and Baekelandt, V. (2015). α-Synuclein strains cause distinct synucleinopathies after local and systemic administration. Nature *522*, 340–344.

Pemberton, S., Madiona, K., Pieri, L., Kabani, M., Bousset, L., and Melki, R. (2011). Hsc70 protein interaction with soluble and fibrillar alpha-synuclein. J. Biol. Chem. *286*, 34690–34699.

Pieri, L., Madiona, K., Bousset, L., and Melki, R. (2012). Fibrillar α-synuclein and huntingtin exon 1 assemblies are toxic to the cells. Biophys. J. *102*, 2894–2905.

Pieri, L., Madiona, K., and Melki, R. (2016). Structural and functional properties of prefibrillar α-synuclein oligomers. Sci. Rep. *6*, 24526.

Pranke, I.M., Morello, V., Bigay, J., Gibson, K., Verbavatz, J.-M., Antonny, B., and Jackson, C.L. (2011). α-Synuclein and ALPS motifs are membrane curvature sensors whose contrasting chemistry mediates selective vesicle binding. J. Cell Biol. *194*, 89–103.

Price, D.L., Rockenstein, E., Ubhi, K., Phung, V., MacLean-Lewis, N., Askay, D., Cartier, A., Spencer, B., Patrick, C., Desplats, P., et al. (2010). Alterations in mGluR5 expression and signaling in Lewy body disease and in transgenic models of alpha-synucleinopathy–implications for excitotoxicity. PLoS ONE *5*, e14020.

Pujadas, L., Rossi, D., Andrés, R., Teixeira, C.M., Serra-Vidal, B., Parcerisas, A., Maldonado, R., Giralt, E., Carulla, N., and Soriano, E. (2014). Reelin delays amyloid-beta fibril formation and rescues cognitive deficits in a model of Alzheimer's disease. Nat. Commun. *5*, 3443.

Qin, Z., Hu, D., Han, S., Reaney, S.H., Di Monte, D.A., and Fink, A.L. (2007). Effect of 4-hydroxy-2-nonenal modification on alpha-synuclein aggregation. J. Biol. Chem. *282*, 5862–5870.

Rammes, G., Hasenjäger, A., Sroka-Saidi, K., Deussing, J.M., and Parsons, C.G. (2011). Therapeutic significance of NR2B-containing NMDA receptors and mGluR5 metabotropic glutamate receptors in mediating the synaptotoxic effects of β-amyloid oligomers on long-term potentiation (LTP) in murine hippocampal slices. Neuropharmacology *60*, 982–990.

Ren, P.-H., Lauckner, J.E., Kachirskaia, I., Heuser, J.E., Melki, R., and Kopito, R.R. (2009). Cytoplasmic penetration and persistent infection of mammalian cells by polyglutamine aggregates. Nat. Cell Biol. *11*, 219–225.

Renner, M., Choquet, D., and Triller, A. (2009). Control of the postsynaptic membrane viscosity. J. Neurosci. *29*, 2926–2937.

Renner, M., Lacor, P.N., Velasco, P.T., Xu, J., Contractor, A., Klein, W.L., and Triller, A. (2010). Deleterious effects of amyloid β oligomers acting as an extracellular scaffold for mGluR5. Neuron *66*, 739–754.

Rey, N.L., Petit, G.H., Bousset, L., Melki, R., and Brundin, P. (2013). Transfer of human α-synuclein from the olfactory bulb to interconnected brain regions in mice. Acta Neuropathol. *126*, 555–573.

Reynolds, N.P., Soragni, A., Rabe, M., Verdes, D., Liverani, E., Handschin, S., Riek, R., and Seeger, S. (2011). Mechanism of membrane interaction and disruption by α-synuclein. J. Am. Chem. Soc. *133*, 19366–19375.

Ross, C.A., and Poirier, M.A. (2004). Protein aggregation and neurodegenerative disease. Nat. Med. *10*, S10–S17.

Rouvinski, A., Karniely, S., Kounin, M., Moussa, S., Goldberg, M.D., Warburg, G., Lyakhovetsky, R., Papy-Garcia, D., Kutzsche, J., Korth, C., et al. (2014). Live imaging of prions reveals nascent PrPSc in cell-surface, raft-associated amyloid strings and webs. J. Cell Biol. *204*, 423–441.

Ruegsegger, C., Maharjan, N., Goswami, A., Filézac de L'Etang, A., Weis, J., Troost, D., Heller, M., Gut, H., and Saxena, S. (2016). Aberrant association of misfolded SOD1 with Na(+)/K(+)ATPase-α3 impairs its activity and contributes to motor neuron vulnerability in ALS. Acta Neuropathol. *131*, 427–451.

Salvatico, C., Specht, C.G., and Triller, A. (2015). Synaptic receptor dynamics: from theoretical concepts to deep quantification and chemistry in cellulo. Neuropharmacology *88*, 2–9.

Sanchez-Pernaute, R., Wang, J.-Q., Kuruppu, D., Cao, L., Tueckmantel, W., Kozikowski, A., Isacson, O., and Brownell, A.-L. (2008). Enhanced binding of metabotropic glutamate receptor type 5 (mGluR5) PET tracers in the brain of parkinsonian primates. Neuroimage *42*, 248–251.

Sanders, D.W., Kaufman, S.K., DeVos, S.L., Sharma, A.M., Mirbaha, H., Li, A., Barker, S.J., Foley, A.C., Thorpe, J.R., Serpell, L.C., et al. (2014). Distinct tau prion strains propagate in cells and mice and define different tauopathies. Neuron *82*, 1271–1288.

Saudou, F., and Humbert, S. (2016). The biology of Huntingtin. Neuron *89*, 910–926.

Saxena, S., and Caroni, P. (2011). Selective neuronal vulnerability in neurodegenerative diseases: from stressor thresholds to degeneration. Neuron *71*, 35–48.

Saxton, M.J., and Jacobson, K. (1997). Single-particle tracking: applications to membrane dynamics. Annu. Rev. Biophys. Biomol. Struct. *26*, 373–399.

Sekimoto, K., and Triller, A. (2009). Compatibility between itinerant synaptic receptors and stable postsynaptic structure. Phys. Rev. E Stat. Nonlin. Soft Matter Phys. *79*, 031905.

Selenica, M.L., Brownlow, M., Jimenez, J.P., Lee, D.C., Pena, G., Dickey, C.A., Gordon, M.N., and Morgan, D. (2013). Amyloid oligomers exacerbate tau pathology in a mouse model of tauopathy. Neurodegener. Dis. *11*, 165–181.

Sevigny, J., Chiao, P., Bussière, T., Weinreb, P.H., Williams, L., Maier, M., Dunstan, R., Salloway, S., Chen, T., Ling, Y., et al. (2016). The antibody aducanumab reduces Aβ plaques in Alzheimer's disease. Nature *537*, 50–56.

Shankar, G.M., Bloodgood, B.L., Townsend, M., Walsh, D.M., Selkoe, D.J., and Sabatini, B.L. (2007). Natural oligomers of the Alzheimer amyloid-beta protein induce reversible synapse loss by modulating an NMDA-type glutamate receptor-dependent signaling pathway. J. Neurosci. *27*, 2866–2875.

Shi, X.D., Sun, K., Hu, R., Liu, X.Y., Hu, Q.M., Sun, X.Y., Yao, B., Sun, N., Hao, J.R., Wei, P., et al. (2016). Blocking the interaction between EphB2 and ADDLs by a small peptide rescues impaired synaptic plasticity and memory deficits in a mouse model of Alzheimer's disease. J. Neurosci. *36*, 11959–11973.

Shrivastava, A.N., Kowalewski, J.M., Renner, M., Bousset, L., Koulakoff, A., Melki, R., Giaume, C., and Triller, A. (2013). β-amyloid and ATP-induced diffusional trapping of astrocyte and neuronal metabotropic glutamate type-5 receptors. Glia *61*, 1673–1686.

Shrivastava, A.N., Redeker, V., Fritz, N., Pieri, L., Almeida, L.G., Spolidoro, M., Liebmann, T., Bousset, L., Renner, M., Léna, C., et al. (2015). α-synuclein assemblies sequester neuronal α3-Na+/K+-ATPase and impair Na+ gradient. EMBO J. *34*, 2408–2423.

Sigal, Y.M., Speer, C.M., Babcock, H.P., and Zhuang, X. (2015). Mapping synaptic input fields of neurons with super-resolution imaging. Cell *163*, 493–505.

Snyder, E.M., Nong, Y., Almeida, C.G., Paul, S., Moran, T., Choi, E.Y., Nairn, A.C., Salter, M.W., Lombroso, P.J., Gouras, G.K., and Greengard, P. (2005). Regulation of NMDA receptor trafficking by amyloid-beta. Nat. Neurosci. *8*, 1051–1058.

Sonati, T., Reimann, R.R., Falsig, J., Baral, P.K., O'Connor, T., Hornemann, S., Yaganoglu, S., Li, B., Herrmann, U.S., Wieland, B., et al. (2013). The toxicity of antiprion antibodies is mediated by the flexible tail of the prion protein. Nature *501*, 102–106.

Stöhr, J., Condello, C., Watts, J.C., Bloch, L., Oehler, A., Nick, M., DeArmond, S.J., Giles, K., DeGrado, W.F., and Prusiner, S.B. (2014). Distinct synthetic Aβ prion strains producing different amyloid deposits in bigenic mice. Proc. Natl. Acad. Sci. USA *111*, 10329–10334.

Surmeier, D.J., Obeso, J.A., and Halliday, G.M. (2017). Selective neuronal vulnerability in Parkinson disease. Nat. Rev. Neurosci. *18*, 101–113.

Suttkus, A., Holzer, M., Morawski, M., and Arendt, T. (2016). The neuronal extracellular matrix restricts distribution and internalization of aggregated Tau-protein. Neuroscience *313*, 225–235.

Syková, E., and Nicholson, C. (2008). Diffusion in brain extracellular space. Physiol. Rev. *88*, 1277–1340.

Takeda, S., Wegmann, S., Cho, H., DeVos, S.L., Commins, C., Roe, A.D., Nicholls, S.B., Carlson, G.A., Pitstick, R., Nobuhara, C.K., et al. (2015). Neuronal uptake and propagation of a rare phosphorylated high-molecular-weight tau derived from Alzheimer's disease brain. Nat. Commun. *6*, 8490.

Tardivel, M., Bégard, S., Bousset, L., Dujardin, S., Coens, A., Melki, R., Buée, L., and Colin, M. (2016). Tunneling nanotube (TNT)-mediated neuron-to neuron transfer of pathological Tau protein assemblies. Acta Neuropathol. Commun. *4*, 117.

Taylor, D.R., Whitehouse, I.J., and Hooper, N.M. (2009). Glypican-1 mediates both prion protein lipid raft association and disease isoform formation. PLoS Pathog. *5*, e1000666.

Tran, H.T., Chung, C.H.-Y., Iba, M., Zhang, B., Trojanowski, J.Q., Luk, K.C., and Lee, V.M.Y. (2014). A-synuclein immunotherapy blocks uptake and templated propagation of misfolded α-synuclein and neurodegeneration. Cell Rep. *7*, 2054–2065.

Triller, A., and Choquet, D. (2008). New concepts in synaptic biology derived from single-molecule imaging. Neuron *59*, 359–374.

Tyedmers, J., Mogk, A., and Bukau, B. (2010). Cellular strategies for controlling protein aggregation. Nat. Rev. Mol. Cell Biol. *11*, 777–788.

Um, J.W., Kaufman, A.C., Kostylev, M., Heiss, J.K., Stagi, M., Takahashi, H., Kerrisk, M.E., Vortmeyer, A., Wisniewski, T., Koleske, A.J., et al. (2013). Metabotropic glutamate receptor 5 is a coreceptor for Alzheimer aβ oligomer bound to cellular prion protein. Neuron *79*, 887–902.

Uversky, V.N. (2003). A protein-chameleon: conformational plasticity of alpha-synuclein, a disordered protein involved in neurodegenerative disorders. J. Biomol. Struct. Dyn. *21*, 211–234.

Valencia, A., Reeves, P.B., Sapp, E., Li, X., Alexander, J., Kegel, K.B., Chase, K., Aronin, N., and DiFiglia, M. (2010). Mutant huntingtin and glycogen synthase kinase 3-beta accumulate in neuronal lipid rafts of a presymptomatic knock-in mouse model of Huntington's disease. J. Neurosci. Res. *88*, 179–190.

van Horssen, J., Kleinnijenhuis, J., Maass, C.N., Rensink, A.A.M., Otte-Höller, I., David, G., van den Heuvel, L.P.W.J., Wesseling, P., de Waal, R.M.W., and Verbeek, M.M. (2002). Accumulation of heparan sulfate proteoglycans in cerebellar senile plaques. Neurobiol. Aging *23*, 537–545.

van Rooijen, B.D., Claessens, M.M.A.E., and Subramaniam, V. (2009). Lipid bilayer disruption by oligomeric alpha-synuclein depends on bilayer charge and accessibility of the hydrophobic core. Biochim. Biophys. Acta *1788*, 1271–1278.

Vargas, L.M., Leal, N., Estrada, L.D., González, A., Serrano, F., Araya, K., Gysling, K., Inestrosa, N.C., Pasquale, E.B., and Alvarez, A.R. (2014). EphA4 activation of c-Abl mediates synaptic loss and LTP blockade caused by amyloid-β oligomers. PLoS ONE *9*, e92309.

Varkey, J., Isas, J.M., Mizuno, N., Jensen, M.B., Bhatia, V.K., Jao, C.C., Petrlova, J., Voss, J.C., Stamou, D.G., Steven, A.C., and Langen, R. (2010). Membrane curvature induction and tubulation are common features of synucleins and apolipoproteins. J. Biol. Chem. *285*, 32486–32493.

Verbeek, M.M., Otte-Höller, I., van den Born, J., van den Heuvel, L.P., David, G., Wesseling, P., and de Waal, R.M. (1999). Agrin is a major heparan sulfate proteoglycan accumulating in Alzheimer's disease brain. Am. J. Pathol. *155*, 2115–2125.

Wang, Y., and Mandelkow, E. (2016). Tau in physiology and pathology. Nat. Rev. Neurosci. *17*, 5–21.

Wang, H.Y., Lee, D.H., D'Andrea, M.R., Peterson, P.A., Shank, R.P., and Reitz, A.B. (2000). beta-Amyloid(1-42) binds to alpha7 nicotinic acetylcholine receptor with high affinity. Implications for Alzheimer's disease pathology. J. Biol. Chem. *275*, 5626–5632.

Wang, D., Govindaiah, G., Liu, R., De Arcangelis, V., Cox, C.L., and Xiang, Y.K. (2010). Binding of amyloid beta peptide to beta2 adrenergic receptor induces PKA-dependent AMPA receptor hyperactivity. FASEB J. *24*, 3511–3521.

Watanabe, N., Araki, W., Chui, D.-H., Makifuchi, T., Ihara, Y., and Tabira, T. (2004). Glypican-1 as an Abeta binding HSPG in the human brain: its localization in DIG domains and possible roles in the pathogenesis of Alzheimer's disease. FASEB J. *18*, 1013–1015.

Wegmann, S., Nicholls, S., Takeda, S., Fan, Z., and Hyman, B.T. (2016). Formation, release, and internalization of stable tau oligomers in cells. J. Neurochem. *139*, 1163–1174.

Wisniewski, T., and Goñi, F. (2015). Immunotherapeutic approaches for Alzheimer's disease. Neuron *85*, 1162–1176.

Wu, J.W., Hussaini, S.A., Bastille, I.M., Rodriguez, G.A., Mrejeru, A., Rilett, K., Sanders, D.W., Cook, C., Fu, H., Boonen, R.A.C.M., et al. (2016). Neuronal activity enhances tau propagation and tau pathology in vivo. Nat. Neurosci. *19*, 1085–1092.

Xie, L., Helmerhorst, E., Taddei, K., Plewright, B., Van Bronswijk, W., and Martins, R. (2002). Alzheimer's beta-amyloid peptides compete for insulin binding to the insulin receptor. J. Neurosci. *22*, RC221.

Yaar, M., Zhai, S., Pilch, P.F., Doyle, S.M., Eisenhauer, P.B., Fine, R.E., and Gilchrest, B.A. (1997). Binding of β-amyloid to the p75 neurotrophin receptor induces apoptosis. A possible mechanism for Alzheimer's disease. J. Clin. Invest. *100*, 2333–2340.

Yamaguchi, H., Maat-Schieman, M.L., van Duinen, S.G., Prins, F.A., Neeskens, P., Natté, R., and Roos, R.A. (2000). Amyloid beta protein (Abeta) starts to deposit as plasma membrane-bound form in diffuse plaques of brains from hereditary cerebral hemorrhage with amyloidosis-Dutch type, Alzheimer disease and nondemented aged subjects. J. Neuropathol. Exp. Neurol. *59*, 723–732.

Yan, S.D., Chen, X., Fu, J., Chen, M., Zhu, H., Roher, A., Slattery, T., Zhao, L., Nagashima, M., Morser, J., et al. (1996). RAGE and amyloid-β peptide neurotoxicity in Alzheimer's disease. Nature *382*, 685–691.

Yanagisawa, K., Odaka, A., Suzuki, N., and Ihara, Y. (1995). GM1 ganglioside-bound amyloid beta-protein (A beta): a possible form of preamyloid in Alzheimer's disease. Nat. Med. *1*, 1062–1066.

Yanamandra, K., Kfoury, N., Jiang, H., Mahan, T.E., Ma, S., Maloney, S.E., Wozniak, D.F., Diamond, M.I., and Holtzman, D.M. (2013). Anti-tau antibodies that block tau aggregate seeding in vitro markedly decrease pathology and improve cognition in vivo. Neuron *80*, 402–414.

Yu, A., Shibata, Y., Shah, B., Calamini, B., Lo, D.C., and Morimoto, R.I. (2014). Protein aggregation can inhibit clathrin-mediated endocytosis by chaperone competition. Proc. Natl. Acad. Sci. USA *111*, E1481–E1490.

Zeng, M., Shang, Y., Araki, Y., Guo, T., Huganir, R.L., and Zhang, M. (2016). Phase Transition in Postsynaptic Densities Underlies Formation of Synaptic Complexes and Synaptic Plasticity. Cell *166*, 1163–1175.e12.

Zhao, W.Q., Santini, F., Breese, R., Ross, D., Zhang, X.D., Stone, D.J., Ferrer, M., Townsend, M., Wolfe, A.L., Seager, M.A., et al. (2010). Inhibition of calcineurin-mediated endocytosis and alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors prevents amyloid beta oligomer-induced synaptic disruption. J. Biol. Chem. *285*, 7619–7632.

Zhou, W., Long, C., Reaney, S.H., Di Monte, D.A., Fink, A.L., and Uversky, V.N. (2010). Methionine oxidation stabilizes non-toxic oligomers of alpha-synuclein through strengthening the auto-inhibitory intra-molecular long-range interactions. Biochim. Biophys. Acta *1802*, 322–330.