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REVIEW

Proteinopathies, a core concept for understanding and ultimately treating degenerative disorders?

Thomas A. Bayer*

The Georg-August-University Göttingen, University Medicine Göttingen, Division of Molecular Psychiatry, Von-Siebold-Strasse 5, 37075 Göttingen, Germany

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Abstract
The current review covers proteinopathies an umbrella term for neurodegenerative disorders that are characterized by the accumulation of specific proteins within neurons or in the brain parenchyma. Most prevalent examples for typical proteinopathies are Alzheimer's disease and Parkinson's disease. In healthy brain, these proteins are unstructured as a monomer, serving most likely as the physiological form. In a disease condition, the unstructured proteins experience a conformational change leading to small oligomers that eventually will aggregate into higher order structures. Prion disease is an exception within the family of proteinopathies as the aggregated prion protein is highly infectious and can self-aggregate and propagate. Recent reports might implicate a prion-like spread of misfolded proteins in Alzheimer's and Parkinson's disease; however there are evident differences in comparison to prion diseases. As proteinopathies are caused by the aggregation of disease-typical proteins with an ordered structure, active and passive immunization protocols have been used to expose model systems to therapeutic antibodies that bind to the aggregates thereby inhibiting the prolongation into higher ordered fibrils or dissolving the existing fibrillar structure. While most of the immunization treatments have been only carried out in preclinical model systems overexpressing the disease-relevant aggregating protein, other approaches are already in clinical testing. Taking the core concept of proteinopathies with conformationally altered protein aggregates into account, immunization appears to be a very promising therapeutic option for neurodegenerative disorders.

1. Introduction on the current status of proteinopathies

The present review focuses on proteinopathies of the central nervous system, although the concept also refers to peripheral cells, tissues and organs. The general principle of proteinopathies is that the proteins change their

*Tel.: +49 551 39 22912.
E-mail address: tbayer@gwdg.de

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conformation thereby gaining toxic activity or losing the normal function. The most prominent type of a typical proteinopathy is Alzheimer's disease (AD) although many more exist as Parkinson's disease (PD), Lewy body disease, prion disease, tauopathies, amyotrophic lateral sclerosis, fronto-temporal lobar degeneration, as well as rare disorders like familial British and Danish dementias and cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). This list is by far not complete just reflecting the heterogeneity of different proteinopathies. Some of the proteinopathies are characterized by a single type of proteinaceous aggregate, others by two different aggregated proteins. Very often proteinopathies are mixed making a definite diagnosis and therapy difficult. Aggregated proteins can acquire amyloid characterics, which is a histological definition having its origins in the 19th century.

Rudolph Virchow, in 1854, introduced and popularized the term amyloid to describe a macroscopic tissue abnormality that exhibited a positive iodine staining reaction (Sipe and Cohen, 2000) giving the name amyloid for "starch-like" according to the chemical reaction he observed. In 1859, Friedreich and Kekulé identified protein as the real molecular nature of the amyloid deposits rather than consisting of cellulose (Sipe and Cohen, 2000). With the advent of new microscopy and histological staining techniques it became apparent that amyloids elicit birefringence in cross-polarized light after staining with the dye congo red and have a fibrillar structure under the transmission electron microscope (Sipe and Cohen, 2000). However, it is now well accepted that not all amyloids are showing these features. For example diffuse Alzheimer Aβ plaques are not congo red positive possibly reflecting an earlier step in the evolution of plaque development. Today, amyloid is often used to describe Aβ amyloid precipitates, i.e. Alzheimer plaques. In the present review, the term amyloid is used to describe all aggregated proteins in its original histological definition (Sipe and Cohen, 2000).

Proteinopathies are diseases triggered by the aggregation of a normal protein having a physiological function. They become pathologically active after changing in size or their three-dimensional shape resulting in self-association, elongation and precipitation in distinct brain areas. The risk of self-association and aggregation, whether or not it is associated with a genetic defect, is greatly increased with proteins that are inherently able to undergo radical changes in their conformation (Carrell and Lomas, 1997). Often several pathological hallmarks of different disorders are found together. One well-known example is the presence of neurofibrillary tangles and Aβ amyloid plaques, which are the main neuropathological changes in AD brain; many AD patients have concomitant synucleinopathy in the brain, which is typical for Lewy body disease (Duyckaerts et al., 2009).

Prions are infectious proteinaceous agents that cause heritable, sporadic and infectious neurological diseases such as Creutzfeldt–Jakob disease in humans, bovine spongiform encephalopathy in cattle and scrapie in sheep (Colby and Prusiner, 2011). The conformational change occurs in the prion protein (PrP), changing it from its normal or cellular form, PrPC, to the disease-causing conformation, PrPSc via self-aggregation and propagation (Colby and Prusiner, 2011). Prions are a special case of proteinopathies as they are infectious and can even cross species barriers. However, recent findings might implicate a prion-like spread of misfolded proteins also in AD (Meyer-Luehmann et al., 2008) and PD (Kordower et al., 2008; Li et al., 2008). Prion disease can be either acquired or genetically driven.

Whether or not other proteinopathies are prion-like is a matter of current scientific debates, especially how such a condition is defined in a strict sense. The evidence for genetic factors is very strong as many of the disorders are closely linked to mutations (Bertram and Tanzi, 2005). The most common risk factor however is advanced age (Walker and LeVine Iii, 2000) and sometimes traumatic brain injury (DeKosky et al., 2010). Intracellular aggregated proteins are common neuropathological features for all proteinopathies including transmissible prion encephalopathies. This suggests that these neurodegenerative diseases might have similar molecular mechanisms. In all cases, proteins aggregate due to a loss in clearance, enhanced production or post-translational modifications resulting in a change in their conformations different from their native condition.

In contrast to all other proteinopathies, prion diseases are transmitted by highly infective misfolded prions. Brundin et al. (2010) argued that protein misfolding can result from native proteins changing their conformations or newly synthesized polypeptides failing to fold properly. They stated that incompletely or incorrectly folded proteins expose hydrophobic amino acid side chains on their surfaces that are normally buried in the interior of the native state. Thus, they become prone to self-association into aggregates that can function as nuclei that recruit additional monomers. The consequence is that oligomers are generated on the expense of monomers. As has been reviewed (Brundin et al., 2010) such protein aggregates can become infectious and are called prions (Prusiner, 1991). Three factors are required for the definition of a prion-typical transmission: (i) the intermolecular interactions between the constitutive molecules are so strong that aggregation is effectively irreversible, (ii) the prions resist the cell clearance machinery and (iii) they need to propagate from one cell to another, in which they recruit non-native polypeptide monomers (Brundin et al., 2010). While there is no doubt that these factors hold true for transmissible prion encephalopathies, the case for AD and PD is less strong. Still, several recent experimental observations have suggested that protein aggregates, might move from affected to unaffected areas of the brain, suggesting that a prion-like transmission of these diseases might exist and could contribute to the anatomical spread of disease pathology. PD patients who had been transplanted with normal embryonic neurons developed disease-typical intracellular alpha-synuclein-positive Lewy bodies in some of the grafted neurons (Kordower et al., 2008; Li et al., 2008). These observations indicate that cell non-autonomous mechanisms are important for the pathogenesis of neurodegenerative diseases with intracellular filamentous inclusions. The intercellular transfer of inclusions made of tau, α-synuclein, huntingtin and superoxide dismutase 1 has been demonstrated, revealing the existence of mechanisms reminiscent of those by which prions spread through the nervous system (Goedert et al., 2010). In the case of AD, such a protein seeding effect has been demonstrated in mice overexpressing the amyloid precursor protein (APP). Aβ-Amyloid extracts derived from brains of AD patients or aged APP transgenic mice were injected into the brain of APP

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