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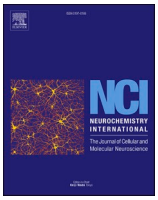

Amyloid polymorphs and pathological diversities

Ronald Melki

Institut Francois Jacob (MIRCen), CEA and Laboratory of Neurodegenerative Diseases, CNRS, 18 Route du Panorama, 92265, Fontenay-Aux-Roses cedex, France

A B S T R A C T

The presence of protein aggregates within the central nervous system is intimately associated to debilitating neurodegenerative diseases. While the aggregation of proteins, that share no primary structure identity, is understandable in different diseases, that of a given protein yielding distinct pathologies is counterintuitive. This short review relates molecular and mechanistic processes to the observed pathological diversity.

1. Introduction

The aggregation of many proteins and polypeptides into assemblies of fibrillar nature is the hallmark of numerous diseases. Tau, A-beta, alpha-synuclein, PrP, huntingtin, serpins, aggregation is for instance intimately associated to tauopathies, such as Alzheimer's disease, synucleinopathies, such as Parkinson's disease, spongiform encephalopathies, such as Creutzfeldt-Jacob disease, Huntington's disease and different forms of dementias. These proteins share no primary structure identity and this may account for the different diseases they cause. However, taken individually, all of these proteins are tightly associated to different diseases. For instance, Tau aggregation is involved in Alzheimer's disease but also Pick's disease, progressive supranuclear palsy, globular glial tauopathy, aging related tau astrogliopathy, chronic traumatic encephalopathy, argyrophilic grain disease, primary age-related tauopathy. Alpha-synuclein aggregation is involved in Parkinson's disease, Lewy body dementia and the two forms of multiple system atrophy. There must be explanations for that. This short review provides plausible molecular and mechanistic events that may account for the observed pathological diversity.

2. Amyloid formation and structural diversity

Most of the proteins listed above are in total or part "natively unfolded", a term used to reflect their dynamics. These proteins in total or part adopt multiple conformation, not necessarily extended, that does not allow determining an average conformation unless upon binding a ligand ranging from a small molecule to a ligand (Ferreon et al., 2009; Frimpong et al., 2010; Weinreb et al., 1996; Eliezer et al., 2001; Uversky 2003; Maiti et al., 2004; Sandal et al., 2008; Anderson et al., 2012; Burre et al., 2013; Lashuel et al., 2013; Theillet et al., 2016; Ulmer et al., 2005; Jeganathan et al., 2008; Mukrasch et al., 2009; Narayanan et al., 2010). The ensemble of tertiary structures or conformational states these dynamic proteins or protein domains populate depends on their primary structure and is immense. Indeed, if we assume that each amino acid residue within a protein or protein domain made of 100 amino acid residues can adopt a limited number of conformations, for example 3 (1 trans and 2 gauche) with only 2 torsions each, the number of possible conformations such a protein or protein domain could adopt would surpass 3^{198} (3^{99x2}) conformations. The different conformations within the ensemble of tertiary structures are in equilibrium (Fig. 1A), meaning that each conformation is populated for a given time (Fersht, 1999). If each conformation is populated for a very small fraction of a second, e.g. 10^{-12} s, it would take a single molecule over the age of the universe to populate this limited set of possible conformations. The concentration and lifespan of each conformation are specific to the tertiary structure and are defined by intramolecular interactions between amino acid residues stabilized by hydrogen bonds, electrostatic and hydrophobic interactions. The latter depend on the amino acid composition of the protein, the distribution of the amino acid residues within the protein primary structure and the chemical and physical conditions surrounding the protein. This is why the ensemble of conformations such a protein or protein domain can explore is several orders of magnitude smaller than the number indicated above. As a consequence, the probability of a dynamic aggregation prone monomeric protein to populate conformers exposing amino acid stretches that allow them to establish well-defined inter-molecular interactions with molecules that are in a compatible conformation is far from negligible at any time. This leads to ordered aggregation.

As upon the crystallization of a protein, the nature of the interactions allowing the formation of the quaternary structures, e.g. dimers, trimers and higher molecular weight oligomeric species between molecules, of a given protein define the stability of the assemblies this protein forms (Oosawa and Asakura, 1975). When a molecule adopts conformations

E-mail address: ronald.melki@cnrs.fr.

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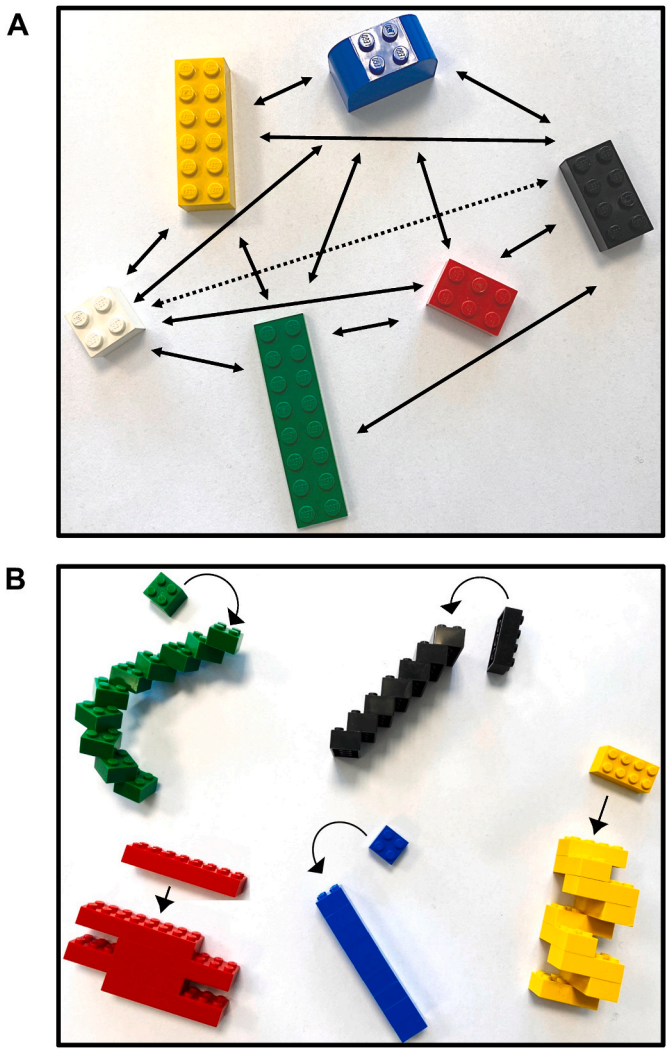

Fig. 1. A, Proteins involved in neurodegenerative diseases such as Tau, A-beta, alpha-synuclein, PrP, huntingtin, serpins, etc … adopt multiple conformations in equilibrium with each other as represented here by bricks of different shapes and colors. The shapes represent the different conformations a polypeptide adopts. The colors are diverse given that when a conformation differ from another, the amino acid stretches exposed at the surface of the protein are distinct. B, A given aggregation prone protein in different conformations (bricks with different shapes) can establish different complementary interactions with molecules in compatible conformation. The nature of the interactions between molecules of a given protein (different ways the bricks are piled up) define the stability of the assemblies this protein forms.

incapable of establishing stable and highly complementary interaction with the seed elongating tips it cannot add on and be subsequently incorporated within the seed (Fig. 1B). However, a given protein in different conformations can establish different complementary interactions with molecules in compatible conformation. Thus, assemblies, including crystals, made of the same protein in different conformations can form (Fig. 1B).

Most of the proteins whose aggregation is associated to neurodegenerative diseases adopt beta-strands secondary structures rich conformations. The distribution of these beta strands is highly dependent on protein primary structure. The establishment of numerous hydrogen bonds between the molecules allows their highly ordered stacking into assemblies of fibrillar shapes named amyloids. The term amyloid signifies starchlike. This term was used in the 19th century to refer to deposits within the brain that stain pale blue with iodine and violet upon treatment with sulfuric acid as do starch deposits in plants. Amyloid fibrils are defined as fibrillar polypeptide aggregates with cross-beta conformation, a structure where the hydrogen bonds between two consecutive sheets are oriented parallel to the main fibril axis while the constituting beta-strands are oriented transversely to the main fibril axis (Astbury and Dickinson, 1935; Makin and Serpell, 2005). This type of structure gives rise to a characteristic pattern of reflections in X-ray diffraction experiments consisting of a conserved 4.6–4.8 Angström meridional spacing and an equatorial spacing of about 10 Angström. The 4.6–4.8 Angström reflection comes from the distance between two hydrogen bonded strands and is invariant as it depends on the geometry of the polypeptide backbone. It is referred to as the "main chain spacing". The equatorial reflection at about 10 Angström comes from the packing distance between two juxtaposed beta-sheets (Sunde et al., 1997; Fandrich and Dobson, 2002). This distance can vary with the polypeptide amino acid composition as it depends on the orthogonal protrusion of the amino acid side chains from the plane of the sheet. It is worth noting that this reflection is not observed when the inter-sheet spacing is not regular.

3. Molecular consequence of amyloid fibrils structural diversity

Most dynamic proteins can populate different beta-strands rich conformations, the stacking of which, following the principles detailed above, yield amyloids with the characteristic 4.6–4.8 and ~10 Angström reflections and additional reflections originating from highly ordered domains stacks, when they exist. The distinct folds an amyloid core of a given fibril adopts defines the surfaces the fibrils expose to the solvent. It also determines whether the fibrillar scaffold is made of a single or multiple protofilaments. This has consequences on fibrils growth rates, nanomechanical properties, processing and degradation by the cellular machinery in charge of their clearance and ligands binding, in particular their cellular interactomes.

Indeed, the different tertiary structures or folds a given amyloid forming protein can adopt define the way the molecules stack into fibrils, the inter molecular interfaces between any two consecutive protein molecules and the number of intermolecular H-bonds within these interfaces (Bousset et al., 2013; Guerrero-Ferreira et al., 2018, 2019; Schweighauser et al., 2020; Zhao et al., 2020; Li Y et al., 2018; Li B et al., 2018; Burger et al., 2021; Fitzpatrick et al., 2017; Falcon et al., 2018; Falcon et al., 2019; Zhang et al., 2020; Shi et al., 2021). This affects mostly fibrils growth through the incorporation of molecules in compatible conformations. Different folds for a given protein define the surfaces of the stacks they form. The latter allow or not defined interactions between different stacks of a protein in the same or different conformations yielding fibrils made of multiple protofilaments. Thus, the intrinsic architectures of fibrils made even from one given protein is defined by the amyloid forming folds its constituting protein populates. This in turn defines the amino acid stretches composing the solvent exposed polypeptide chains and their distribution in space at the external surfaces of the fibrils, the surfaces through which they interact with ligands ranging from small molecules to cell components (Landureau et al., 2021; Caroux et al., 2021).

4. Amyloid structural diversity and differential tropism

The amino acid residues and peptide chains exposed to the solvent at the surface of amyloid protein fibrils involved in neurodegenerative diseases determine what cell type and cellular components they interact with. Indeed, the presence of receptors and their density at the surface of neuronal cells define whether an amyloid fibril can bind to a given cell and the tropism of the fibrils to the cells. These receptors are extracellular matrix, phospholipids and membrane proteins. Amyloid protein fibrils surfaces also define whether they may be post-translationally modified and as a consequence their interactomes that depend on post-translational modifications.

Indeed, Amyloids binding to the cell membrane has been shown to

affect membrane fluidity and geometry/curvature (Smith et al., 2009). The lateral diffusion of amyloids in the plane of the plasma membrane together or independently of membranous components such as receptors, channels, adhesion molecules, contributes to the redistribution and/or coalescence of protein partners at the surface of the cell (Rossy et al., 2014; Shrivastava et al., 2017).

The different surfaces amyloid fibrils expose to the solvent define their interactome. A-beta and alpha-synuclein interact with the α3 subunit of neuronal sodium/potassium pump (Shrivastava et al., 2015; Ohnishi et al., 2015) while A-beta amyloids only to interact with 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), Ephrin B2 receptor (Cissé et al., 2011) and PrPc-mGluR5 complex (Lauren et al., 2009; Renner et al., 2010; Um et al., 2013; Haas et al., 2014; Haas and Strittmatter, 2016; Hu et al., 2014; Casley et al., 2009; Lim et al., 2013; Shrivastava et al., 2013). Furthermore, while α-synuclein amyloids interact with 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 (Bellani et al., 2014), A-beta amyloids do not. This clearly shows that the surface properties of distinct amyloid proteins define their interaction with partner proteins at the surface of neuronal cells. As structurally distinct amyloid fibrils made of one given protein expose different amino acid residues and peptide chains to the solvent (Landureau et al., 2021; Caroux et al., 2021) it appears that they will interact with different ensembles of protein partners at the surface of neuronal cells. The same holds true upon post-translational modifications of amyloid protein fibrils surfaces.

5. Relationship between amyloid fibrils diversity and the nature of pathology

After take up by neuronal cells, amyloids made of distinct proteins involved in different neurodegenerative diseases interact with cytosolic components ranging from organelles to proteins which nature is dictated by their surfaces. The same is true for structurally distinct amyloids made of one given protein. Thus, distinct amyloids redistribute and or trap into a non-functional state different partner proteins. They also compromise to different extents the integrity of intracellular membranous compartments (Flavin et al., 2017; Gribaudo et al., 2019). In addition, as the probability with which the different tertiary structures or folds compatible with the amyloid seed are populated defines the rate at which they elongate and multiply, amyloid fibrils structure determines the rate at which the functional form of an amyloid forming protein is exhausted in cells after aggregation and contributes to the speed at which a pathology progresses with time and its nature. The lateral surfaces of amyloids determine their capacity to bundle thus masking proteolytic cleavage sites which in turn defines their resistance to clearance by the cellular degradation machineries.

As detailed above, amino acid stretches exposed on the sides of different amyloids involved in neurodegenerative diseases define their interactomes. The full interactome of pathogenic protein aggregates whether in the cytoplasm or at the plasma membrane is far from being known. A number of extracellularly exposed membranous components have been identified. One kind of α-synuclein fibrillar amyloid has been shown to bind neurexin-subunits, α3-Na+/K+ -ATPase, amyloid β precursor-like protein 1, neurexins, apolipoprotein E, agrin and the Glucose Related Protein of 78 kDa (Mao et al., 2016; Shrivastava et al., 2015; Bellani et al., 2014). Tau 1N3R and 1N4R amyloid fibrils interact both with muscarinic receptors (Gomez-Ramos et al., 2008), Na+/K+ -ATPase, glutamate AMPA and NMDA receptors, glypicans, neurexins, plasma membrane calcium transporting ATPase, voltage dependent anion selective channel proteins with notable differences in the interactomes of 1N3R and 1N4R Tau amyloids (Shrivastava et al., 2019). One of the numerous Aβ amyloid polymorphs bind mGluR5s, α7-nicotinic acetylcholine receptors, leukocyte immunoglobulin-like receptor B2, α3-Na+/K+ -ATPase, Ephrin B2 receptor and PrPc (Casley et al., 2009; Lim et al., 2013; Shrivastava et al., 2013; Wang et al., 2000; Dineley et al., 2001; Snyder et al., 2005; Dziewczapolski et al., 2009; Kim et al., 2013; Ohnishi et al., 2015; Cissé et al., 2011; Lauren et al., 2009). Further identification of fibrils interactomes will allow assessing modulators of aggregation by rapid screening methods (Hideshima et al., 2022). It will allow also a better understanding of their spread patterns as the presence and abundance of these proteins on the surface of neuronal cells define the tropism of distinct amyloid fibrils released from dying cells, where they form, for different neuronal cell populations within the central nervous system. In other words their target cell populations.

6. Conclusion

Altogether the surfaces of structurally distinct amyloid fibrils made of a given protein or proteins sharing no primary structure identity defines their interactomes and as a consequence tropism for defined neuronal populations within the central nervous system. This can lead to different distributions in distinct neurodegenerative diseases. The intrinsic architecture of amyloid fibrils and the structure their constituting protein adopt within the fibrillar scaffold define their ability to bundle, be post-translationally modified and grow by incorporation and depletion of the cellular pool of their functional cellular form, e.g. their resistance to the cellular clearance machinery and rate of multiplication, respectively. As diverse cells within the central nervous system differ among other things by the membrane proteins they express, differential binding of distinct polymorphs may lead to the pathophysiological characteristics of distinct pathologies. Crucial insights into the relationship between amyloid polymorphism and pathological diversities will come from the thorough identification of structurally distinct amyloids made of one given or different proteins involved in diverse neurodegenerative diseases.

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