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Review

Living with the enemy: from protein-misfolding pathologies we know, to those we want to know

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ABSTRACT

Conformational diseases are caused by the aggregation of misfolded proteins. The risk for such pathologies develops years before clinical symptoms appear, and is higher in people with alpha-1 antitrypsin (AAT) polymorphisms. Thousands of people with alpha-1 antitrypsin deficiency (AATD) are underdiagnosed. Enemy-aggregating proteins may reside in these underdiagnosed AATD patients for many years before a pathology for AATD fully develops. In this perspective review, we hypothesize that the AAT protein could exert a new and previously unconsidered biological effect as an endogenous metal ion chelator that plays a significant role in essential metal ion homeostasis. In this respect, AAT polymorphism may cause an imbalance of metal ions, which could be correlated with the aggregation of amylin, tau, amyloid beta, and alpha synuclein proteins in type 2 diabetes mellitus (T2DM), Alzheimer's and Parkinson's diseases, respectively.

1. Introduction

A broad range of human diseases arises from defective protein folding- a delicate and complex process that is susceptible to errors resulting in misfolding and successive aggregation. These pathological conditions are generally called misfolding or conformational protein diseases. Abnormal proteins can be present in different organs with intra or extracellular localizations and conformations but the similarities in their appearance suggest common pathogenetic principles (Aigelsreiter et al., 2007; Kokotidou et al., 2020). Nowadays, an increasing number of diseases are correlated with the self-association and the consequent tissue accumulation of misfolded proteins (Iadanza et al., 2018). Among these are serpinopathies, Alzheimer's, Parkinson's and Type 2 Diabetes Mellitus diseases (Ekeowa et al., 2010).

Alpha-1 antitrypsin deficiency (AATD) is one of the best-known misfolding protein pathologies and is considered a prototype of misfolded protein diseases. Only 20% of the individuals carrying the AAT mutated protein manifest pathological evidences, and in this context, Silverman, Pak and Permulter underlined three conceptual paradigms that have led to major advances in understanding the clinical manifestations of protein misfolding diseases and to novel therapeutic strategies (Silverman et al., 2013). The first paradigm involves the causes of these diseases: 'loss-of-function' or toxic 'gain-of-function', where the latter mechanism is attributable to the pathologic activity of the mutant protein itself and/or to the effect of its mislocalization. A second paradigm comes from several protective biological mechanisms (proteostasis), such as the ubiquitin-dependent proteasomal pathway or the autophagic response able to degrade abnormal proteins. The third paradigm applies only when the clinical manifestations occur, i.e., when the pathological effects of the misfolding proteins overwhelm the proteostasis protective

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response. A sort of 'tug-of-war' between all these phenomena, influenced by several factors, begins with the attempt to limit the pathological consequences of both the reduction in protein activity and the excess of misfolding proteins that are ready to be converted from their soluble functional states into highly organized aggregates.

AATD is a unique protein misfolding disease that causes pathology by loss-of-function in one organ (in lung leading to chronic obstructive pulmonary disease (COPD)), and disorders by toxic gain-of-function in another organ (in liver leading to hepatic fibrosis and carcinoma) (Silverman et al., 2013). Moreover, the proteotoxic effect of intra-cellular α1-antitrypsin (AAT) accumulation in the liver has some characteristics in common with other protein misfolding diseases like Alzheimer's, Parkinson's and T2DM. For this reason, the therapeutic strategies used in AATD could prevent or delay the proteotoxity pathological progression observed in different conformational diseases (Lomas, 2013).

Almost 20 years has passed since Carrell and Lomas (Carrell and Lomas, 2002) proposed AATD as a model for conformational diseases and shown similarities between peptide aggregates of mutant serpins (AAT and neuroserpin) and β-amyloid peptide of Alzheimer's disease. Nowadays, we have more scientific data to support their hypothesis, and even extend it to type 2 diabetes mellitus (T2DM), classified recently as a misfolding protein disease (Mukherjee et al., 2015). Moreover, we can hypothesize that conformational diseases are not distinct pathologies but the same pathological state that is correlated with AAT polymorphism, and develops in different tissues at different stages of life. In this context, misfolding protein disease could be recognized at an early stage and treated with one therapeutic strategy.

In this perspective, we first present the crosstalk between AATD, diabetes and neurodegenerative disorders based on clinical data in the literature. We discuss factors affecting misfolding protein diseases with particular attention to metal ion homeostasis. We present the 'tug-of-war' in AATD, T2DM and neurodegenerative disorders and linkages between them. Finally, we discuss the pharmacotherapy strategies for AATD, which were also effective in the treatment of T2DM and neurodegenerative disorders.

1.1. Cross talk between AATD, diabetes and neurodegeneration

Alpha-1 antitrypsin deficiency (A1AD or AATD) is a genetic disorder caused by a mutation in the SERPINA1 gene that results in decrease of alpha-1 antitrypsin (A1AT or AAT), and may result in lung disease or liver disease. Approximately 1 in 2500 individuals worldwide has AATD (Hazari et al., 2017), and about 116 million people carry a copy of the S or Z allele (de Serres, 2002). In Europe, 1 out of 10 people is a carrier of one of two mutations in AAT (Jeppsson, 1976). Nevertheless, AATD is under diagnosed (Luisetti and Seersholm, 2004), with over 100,000 people in Europe estimated to have severe AATD without proper recognition (Torres-Durán et al., 2018). Following recommendations, quantitative serum AAT measurement in stable chronic obstructive pulmonary disease (COPD) patients is used as an initial screening test (Casas et al., 2015), where 1.04 g/L is a borderline value for detecting AATD individuals with a negative predictive value of 99.8% (Greulich et al., 2017). Individuals heterozygous for the S or Z allele (MZ or MS) have 55–80% of normal plasma AAT levels (Mulgrew et al., 2007), and in the cases where AAT concentrations are lower than the reference range, additional phenotyping and/or genotyping studies should be performed (McElvaney, 2015).

AATD patients are highly heterogeneous and neither AAT serum concentrations nor phenotype are efficient in the identification of patients prone to developing severe lung or liver disease (Fregonese and Stolk, 2008). Moreover, the clinical course of AATD-related liver disease is highly variable and it is still unknown why some individuals develop AATD-related liver disease while others do not (Townsend et al., 2018). Liver dysfunction symptoms occur in almost 50% of ZZ children. Before the age of eighteen, 5% of them develop cirrhosis and dreadful diseases, while 8–10% of a subpopulation develop liver disease over the first 40 years of life (Piitulainen et al., 2005). The liver pathology worsens later in life, and adults with liver disease provoked by AATD require liver transplantation (Silverman et al., 2013).

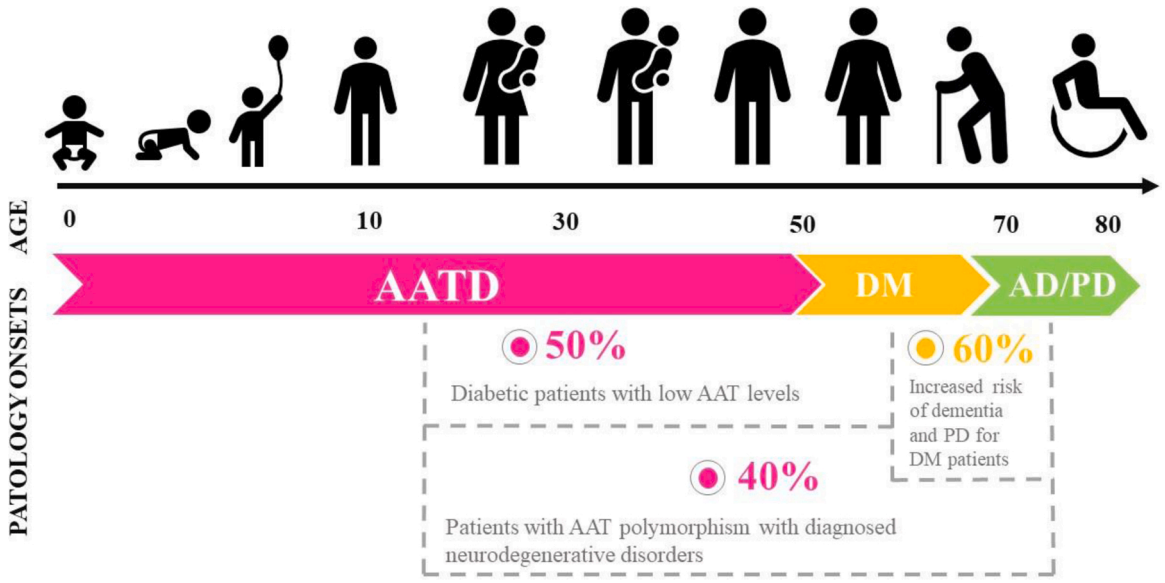
Clinical studies of the last 20 years showed that AATD also predisposes individuals to a wide variety of diseases, associated not only to lung and liver (Cortes-Lopez and Barjaktarevic, 2020) but also other organs (Jezela-Stanek and Chorostowska-Wynimko, 2019). Noteworthy, AATD shares characteristics with the aging process causing organ dysfunction, including emphysema and airflow obstruction, inflammation, immunosenescence and proteostasis dysfunction (Crossley et al., 2019). Studies conducted in 2008 showed that individuals with AAT deficiency genotypes (specifically MZ, MS and FM) and consequent low AAT levels (< 1.0 g/L) are about 50% higher in the diabetic (Scheme 1) compared with the control group (Sandström et al., 2008). In addition, polymorphism of AAT was found in more than 40% of patients with diagnosed neurodegeneration disorders (Scheme 1), and influenced clinical symptoms, and the age and progress of the disease (Schmechel et al., 2006).

Diabetes mellitus (DM) is a chronic disease characterized by progressive loss of β-cell function and β-cell mass, which result in reduced insulin excretion, thus high blood glucose levels (hyperglycemia). According to the International Diabetes Federation, 463 million adults were diagnosed with diabetes in 2019 (http://www.diabetesatlas.org/), caused by either impaired insulin secretion, or the resistance of tissue actions of insulin, or both (Chaudhury et al., 2017). The most commonly cited factors influencing DM progression are genetic, environment, lifestyle, diet and the microbiome (Wu et al., 2014).

Over time, DM can lead to serious damage to the heart, blood vessels, eyes, kidneys, and nerves (Chaudhury et al., 2017; Harding et al., 2019; Sami et al., 2017). Dementia, the most prevalent neurodegenerative disorder, is one of the common complications of DM (Davis et al., 2017). A cohort of 14 studies, with over 2.3 million individuals showed that diabetes was associated with a 60% increased risk (Scheme 1) of any dementia in both sexes (but with higher prevalence in women (Chatterjee et al., 2016)), and higher prevalence of COPD (5.87% vs 3.74%). Another retrospective study conducted on 36,294 patients showed that the incidence density rate of Parkinson's disease (PD) was 1.36-fold higher in DM (23% increased risk of PD in all DM patients), again with increased prevalence in women (Yang et al., 2017).

Alzheimer's disease is the most frequent dementia, accounting for 70% of all cases in Americans (Plassman et al., 2007). World-wide numbers of older adults with dementia is increasing rapidly: there are 4.2 million adults just in the US, while there are 44.3 million people around the world suffering and needing treatments and care (Langa, 2015). It is estimated that AD affects 1 in 8 persons over 65 years old (Association, 2010). Factors affecting AD include low education, socially engaging, or physical activities (Borenstein et al., 2006), hypertension, type 2 diabetes (T2DM), and obesity (Kalaria et al., 2008). Genetic variation is a rare cause of AD (less than 5%), and these inherited forms of Alzheimer's develop earlier in individuals, sometimes already in their thirties (Association, 2008; Kalaria et al., 2008).

Parkinson's disease affects around 3% of the population aged 65 and above, and up to 5% of the population aged 85 and above (Cerri et al., 2019). The average age at which the illness starts is 60 years, and the average lifespan after PD diagnosis is 15 years (Draoui et al., 2020). PD's global prevalence more than doubled between 1990 and 2016, affecting 6.1 million individuals globally in 2016 compared to 2.5 million in 1990 (Dorsey et al., 2018b). The number is expected to reach more than 12 million before 2040, primarily due to aging, and could well surpass 17 million considering rising lifespans and reductions in smoking and environmental exposure due to industrialization, as reported by Dorsey et al. (Dorsey et al., 2018a). Parkinson's disease displays complex regional and ethnic variability in mortality, epidemiology, and clinical manifestations, and the causes of this variability remains unknown (Ben-Joseph et al., 2019, 2020). Furthermore, men present a higher risk of developing the disease, however it progresses more rapidly in women



Scheme 1. Correlation and percentage incidence between AAT polymorphism, T2DM and neurodegenerative disorders.

(Cerri et al., 2019; Dexter and Jenner, 2013).

The principal cause of PD is aging and can be related to certain environmental factors such as pesticide exposure, rural life, and exposure to some toxic substances. While genetics drive a significant percentage of Parkinson's disease (Table 1), other factors are more controversially correlated to PD, such as smoking, caffeine, and cholesterol-lowering drugs (Balestrino and Schapira, 2020). Diabetes is also a risk factor for Parkinson disease development. Onset of diabetes before the onset of PD appears to be a risk factor for more severe PD symptoms (Cereda et al., 2012). Nearly 60% of Parkinson's disease patients are insulin resistant (Martinez-Valbuena et al., 2018) (Scheme 1), and a retrospective cohort study on more than 2 mln individuals with diagnosed T2DM showed significantly elevated rates of PD following T2DM (De Pablo-Fernandez et al., 2018).

The analysis of the literature data on AATD, T2DM, AD and PD presented here reveals a correlation and sequential mechanism of pathology onsets (Scheme 1). The common characteristic of these pathologies is the influence of environmental factors over genetic factors, and biochemical pathways of misfolding proteins. The environmental factors define physico-chemical parameters in the body that extend beyond the physiological range leading to proteosome disfunction and development of misfolding protein diseases (MPDs).

2. Factors affecting protein misfolding and aggregation

Protein misfolding conditions can be described precisely by physico-chemical parameters (pH, temperature, ionic strength, protein concentration, pressure) (Poulson et al., 2020), and can be influenced by environmental (Scheme 2) and/or genetic factors, which shift such parameters out of the physiological range. When the physico-chemical parameters change rapidly and significantly, the protein aggregation process leads to immediate pathological results, which are relatively easy to diagnose and have a good chance of being cured. If the parameters change only slightly but continue for a prolonged time, the protein aggregation process slows down and the symptoms of the pathological state only develop after months or even years. In this case, it is hard to immediately diagnose the disease, and the pathological outcomes can be irreversible and incurable.

Proton concentration (pH) is one of the factors (Scheme 2) that particularly affects the stability of peptides, and can accelerate or slow down the rate of aggregation (Jha et al., 2014; Raman et al., 2005). Even a slight deviation from the protein isoelectric point significantly changes the overall charge of the protein (Cromwell et al., 2006), and impairs the charge dislocation on the surface of the molecule. For instance, a higher surface charge reduces the rate of protein aggregation in water, while it enhances the electrostatic repulsion between positively charged proteins (Cromwell et al., 2006; Engelhardt et al., 2013). Noteworthily, chronic exposure to high pCO_2 in the atmosphere reduces blood pH even to 0.4 units (Schaefer, 1961) and likely leads to proteome dysfunction (Duarte et al., 2020).

Protein aggregation is also a temperature-dependent process (Scheme 2). Increasing temperature leads to a faster molecular collision rate and hydrophobic interaction frequency, thus augmenting the aggregation rate (Speed et al., 1997). In addition, higher temperatures alter the protein's secondary structure leading to abnormal aggregation behaviour (Vermeer and Norde, 2000).

Metal ions (Scheme 2) are other amyloidogenesis-promoting factors. Moreover, metal complexes with proteins and peptides add new electrochemical and spectroscopical properties to amyloids. In addition, metal adducts significantly influence amyloid structure and morphology, not only due to metal/protein complex formation, but also due to significant lowering of the pH in the presence of free metal ions (Abdelrahman et al., 2020). Not surprisingly, metal dyshomeostasis is reported in misfolding-protein diseases.

2.1. *Metal dyshomeostasis in misfolding protein pathologies*

Metal dyshomeostasis in neurodegeneration (Li et al., 2017) and diabetes (Cooper et al., 2005; Khan and Awan, 2014) is a well-established phenomenon, even though the etiology is unknown. Moreover, it is still debatable whether the unbalance of the essential metal ions in the pathological states is a cause or a consequence of adaptive mechanisms during disease development, which is followed by the overexpression of metal-binding proteins (Alghrably et al., 2020). Abnormal concentrations of such proteins, particularly at lower than physiological pH (due to the presence of free metal ions), lead directly to protein aggregation. Recently, the metal binding sites on the main peptides involved in neurodegeneration and diabetes were reviewed (Abdelrahman et al., 2020). The clear cross-talk between iron metabolism and Alzheimer's, Parkinson's and Diabetes diseases are reviewed elsewhere (Rouault, 2013) (Berg and Hochstrasser, 2006) (Fernández--Real et al., 2002).

Metal chelation therapy has been demonstrated to provide relief and amelioration in neurodegeneration (Clayton, 2017) and diabetic

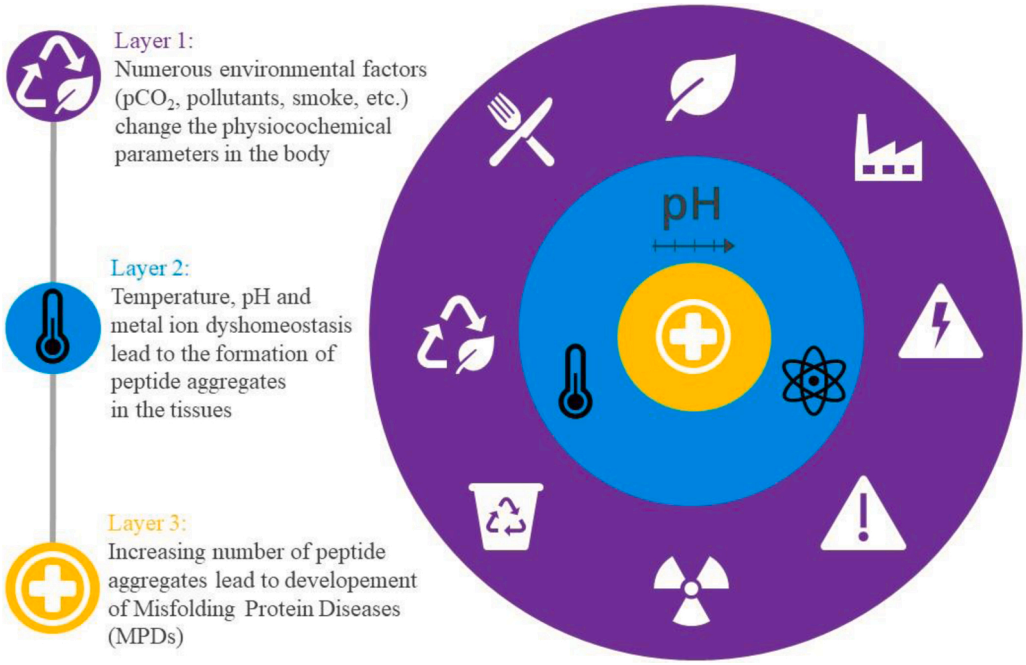
Table 1
Characteristics of peptides involved in protein-misfolding pathologies.

Name of protein	Alpha-1 antitrypsin (AAT)	Tau	Amyloid beta (Aβ)	Alpha-Synuclein (α-Syn)	Human Islet Amyloid Polypeptide (hIAPP)
Alternative name	SERPINA1, A1A, A1AT, PI, PI1, PRO2275, alpha1AT, serpin family A member 1, nNIF	microtubule associated protein tau (MAPT), DDPAC, FTDP-17, MAPTL, MSTD, MTBT1, MTBT2, PPND, PPP1R103,		SNCA, NACP, PARK1, PARK4, PD1	DAP, IAP
Pathology	Alpha-1 antitrypsin Deficiency (AATD)	Alzheimer's Disease (AD)		Parkinson's Disease (PD)	Type 2 Diabetes Mellitus (T2DM)
Chromosom location	14 Gene: SERPINA1	17 Gene: TAU	21 Gene: APP	4 Gene: SNCA	12 Gene: IAPP
Mutations	Different mutations in the serine proteinase inhibitor family lead to serpinopathies. These include the dementia FENIB (mutations in neuroserpin), thrombosis (mutations in antithrombin), angioedema (mutations in C1-inhibitor), and emphysema (mutations in α1-antichymotrypsin). α1-antitrypsin is an acute phase secretory glycoprotein that inhibits neutrophil proteases (e.g. elastase)(Vignaud et al., 2015). Z allele (Glu^{342}→ ΔLys^{342}; GAG →AAG); MMineralSprings (Gly^{67}→Glu^{67}; GGG→GAG); leads to the distortion between the RCL and β-sheet A and subsequent polymerization Rare variants: MMalton (ΔPhe^{52}); Siiyama (Si)-mutation (Ser^{53}→Phe^{53}; TCC→TTC); I-mutation (Arg^{39}→Cys^{39}; CGC→TGC); S-mutation (Glu^{264}→Val^{264}; GAA→GTG); Brescia (Br)-mutation (Gly^{225}→Arg^{225}; GGC→CGG); King's (K)-mutation (His^{334}→Asp^{334}; GAT→CAT)	Mutations are responsible for decreasing the binding affinity of tau to microtubules making the protein more prone to aggregation. This is particularly pronounced for mutations that enhance the β-sheet propensity in the regions of the two hexapeptide motifs. Genetic studies demonstrated that missense mutations (for example, ΔK280, V337 M, P301 L, R406W) are pathogenic for frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17), which is characterized by the presence of prominent neurofibrillary tangles (NFTs) and neurodegeneration (Vignaud et al., 2015). Missense mutations: ΔK280; V337 M; P301 L; R406W.	D7H mutation increases oligomeric Aβ42 and alters properties of Aβ-zinc/copper assemblies (Chen et al., 2012b). The APP717 mutation was correlated with Aβ species within plaques containing mostly Aβ42 (43) with relatively low amounts of Aβ40. In the APP670/671 mutation, the major peptide in plaques is also Aβ42(43), although the proportion of plaques containing Aβ40, and the total Aβ load is similar to that in sporadic Alzheimer's disease (Chen et al., 2012b). The 'Dutch mutation' at position 693 near the a-secretase site results in heredity- neurotoxicity in AD is fibrillar amyloid, with formation of senile plaques a typical but not invariable downstreamtary cerebral haemorrhage with amyloidosis-Dutch type The 'Dutch mutation' at position 693 near the α-secretase site results in hereditary cerebral haemorrhage with amyloidosis-Dutch type. The 'Flemish mutation', at position 692, produces a phenotype which combines features of Alzheimer's disease with those of hereditary cerebral haemorrhage with amyloidosis. Half of early onset familial AD have one of over 40 missense mutations in the presenilin 1 gene on chromosome 14. Such mutations increase the ratio of Aβ42(43)/ Aβ40(Storey and Cappai, 1999).	Familial mutations: A531, A30 P, E46 K, G51D, H50Q. Genetic mutations in SNCA, LRRK2, VPS35, PRKN, PINK1, DJ-1 and GBA have been confirmed to be highly penetrant causes of PD (Bandres-Ciga et al., 2020). DJ-1, PRKN and PINK1 have been implicated in mitochondrial and mitophagy function. GBA, which encodes for the lysosomal enzyme beta-glucocerebrosidase, represents the most common genetic factor associated with PD (Straniero et al., 2020), and, in addition to LRRK2 and VPS35, their mutations are implicated in lysosomal and trafficking pathways (Blauwendraat et al., 2020). The N-terminal amphipathic region (1-30 aa) contains the familial PD mutations, A531, A30 P, E46 K, G51D and H50Q (Doherty et al., 2020; Proukakis et al., 2013). Indeed, α-syn mutants A531 and A30 P have been reported to bind to the lysosomal membrane of the chaperone-mediated autophagy system, which is the selective degradation pathway of wild-type α-syn and serves as absorption blockers for their degradation (Cuervo et al., 2004).	The substitution of serine-to-glycine at position 20 (S20 G) of the human amylin gene is a single genetic mutation in amylin which is implicated in the familial, early-onset form of T2D (Sakagashira et al., 1996). This mutation makes amylin more vulnerable to form fibrils, induces apoptosis, and reduces the number of β-cells in pancreatic islets (Meier et al., 2016). It has also been suggested that S20 G hIAPP aggregates faster than wild-type hIAPP based on findings in cell-free systems (Meier et al., 2016). Moreover, studies using synthetic hIAPP peptides or plasmid transfection in cell lines suggest that the S20 G mutation makes hIAPP more toxic (Cao et al., 2012).
Length	394 aa	758 aa	36-46 aa	140 aa	37 aa
Posttranslational modifications	Glycosylated (N-acetylglucosamine, mannose, galactose and sialic acid) at Asn46, Asn83 and Asn247	Phosphorylation at serine-proline (SP) or threonine-proline (TP) motifs (Biernat et al., 1993; Bramblett et al., 1993; Drechsel et al., 1992); other post-translational modifications such as glycosylation, glycation, prolyl-isomerization, cleavage		Phosphorylation (Ser^{129};~90% (Rocha et al., 2018)), ubiquitination, truncation, nitration, DA modification that impact the aggregation of α-syn and their pathogenesis in PD (Barrett and Greenamyre, 2015).	Amidation of COOH terminal and disulfide bridge formation

(*continued on next page*)

Table 1 (*continued*)

Name of protein	Alpha-1 antitrypsin (AAT)	Tau	Amyloid beta (Aβ)	Alpha-Synuclein (α-Syn)	Human Islet Amyloid Polypeptide (hIAPP)
		or truncation, nitration, polyamination, ubiquitination, sumoylation and oxidation (Martin et al., 2011).			
pI	4.5-5.5 (Hutton et al., 1998)	5.5-6.5 (Liu et al., 1991)	5.3 (Hortschansky et al., 2005)	4.7 (Pinheiro and Ventura, 2019)	8.8 (Azzam et al., 2018)
Function	The serpin superfamily of proteins (Gooptu and Lomas, 2009) are involved in coagulation, inflammation, fibrinolysis, and the complement cascade (Gettins et al., 1993; Potempa et al., 1994; Travis, 1983). The primary role of AAT is to prevent extracellular matrix degradation by neutrophil elastase (NE) in the lungs and regulate inflammation processes.	Its major biological function is to promote the assembly and stabilization of neuronal microtubules (MT), particularly in axons (Allen et al., 1974).	Different functions have been associated with APP, including: metal ion homeostasis (copper and zinc), regulation of neurite outgrowth and/or synaptic plasticity, mediation of cell–matrix and cell–cell interactions, regulation of cell proliferation, differentiation and survival, neuroprotection and regulation of blood coagulation (Storey and Cappai, 1999)	Physiologically, α-syn exhibits molecular chaperone characteristics and assists in folding and refolding of synaptic proteins SNAREs, which is essential for the release of neurotransmitters at the neuronal synapse (Drubin and Kirschner, 1986). α-syn regulates dopamine neurotransmission (Bonini and Giasson, 2005). Moreover, it plays a role in normal mitochondrial and lysosomal function, synaptic plasticity and transmission (Cheng et al., 2011), in dopamine metabolism (Riederer et al., 2019), and it binds to tubulin to promote microtubule formation (Weis et al., 2019).	Inhibitor of the appearance of glucose in plasma (Pittner et al., 1994).



Scheme 2. Circular diagram linking environmental factors with physicochemical parameters of the protein aggregation process, and successive development of misfolding protein diseases (MPDs).

pathology (Lu et al., 2007), but the use of metal-chelating drugs without knowledge of the metal dyshomeostasis etiology is risky and can lead to worsening of the condition over time. Treatment of metal toxicity can be achieved efficiently using a second metal that competes for uptake/-transport, or metal binding sites. Indeed, the therapy of zinc supplementation to treat copper toxicity in Wilson's patients (Brewer, 2001) produced promising results by avoiding the metal-chelating drug toxicity due to the lack of metal selectivity of such drugs (Flora and Pachauri, 2010).

Biologically important ions include six transition metals: manganese, iron, cobalt, copper, zinc and molybdenum. Some of these play essential roles in group transfer reactions such as glycosylation and phosphorylation (Clayton, 2017). Among the essential metal ions, iron, copper and zinc are more likely to be associated with neurodegeneration and diabetes principally due to their higher content with respect to other metals. Iron is one of the most abundant metal ions in the human body, and is highly toxic when present in the free ion form due to its high redox potential and reactive oxygen species production in the Fenton reaction. Ferroptosis is an iron-dependent cell-death process particularly involved in neurodegeneration pathology (Masaldan et al., 2019). Copper is the second essential metal ion with biologically relevant redox potential. Nevertheless, it is not involved in ferroptosis (Dixon et al., 2012). Its

toxic action is associated with reactive oxygen species (ROS) production (Gaetke and Chow, 2003) and increased aggregation of copper-binding proteins (Tamás et al., 2014). Zinc has no redox potential but has a similar metal-coordination pattern with peptides as copper. Even if the stability of zinc/peptide complexes is lower than their copper counterparts, zinc ions can efficiently compete with copper ions for metal binding sites when in excess (the second most abundant metal ion after iron), and could prevent copper-mediated toxicity. Furthermore, zinc deficiency in plasma (Ventriglia et al., 2015) has been reported next to the overload of other metals, such as copper and iron (e.g. in Alzheimer's patients) (Guan et al., 2017). The exact molecular mechanisms of metal ion toxicity are described elsewhere (Bellingham et al., 2015; Li et al., 2017).

Published data analyses of metal content in tissues and fluids in different pathological states is characterized by very high heterogeneity between studies, either in demographic terms or in methodological approaches. Nevertheless, some general conclusions can be drawn. Serum zinc (Ventriglia et al., 2015) and iron (Tao et al., 2014) are significantly decreased in Alzheimer's disease (AD) patients compared with healthy controls, while their levels in cerebrospinal fluid (CSF) do not differ between AD patients and healthy individuals. In contrast, serum copper levels were significantly higher in AD patients than in healthy controls (Wang et al., 2015). Copper concentrations were significantly lower in serum of PD patients, while levels of Fe and Zn in blood and CSF of patients and controls were similar, with a slight increase of Zn and Fe in blood and a decrease of Fe in CSF in patients (Forte et al., 2004). Patients with T2DM have higher copper content in serum, while zinc levels remain unchanged compared to healthy individuals (Bozkurt et al., 2013).

Regarding metal content analysis in tissues closely related to the pathology, brain analysis of AD patients showed lower Cu and Zn concentrations, while iron levels were comparable to the control group (Jackson et al., 2013). Nevertheless, there were significant differences when analyzing different regions of the same organ. For example, in frozen brain samples from deceased Parkinson's patients, there were no changes in the total iron and copper levels in any region, except for the substantia nigra where a 31-35% increase in total iron and 34-45% decrease in total copper were found. Zinc levels were also increased in the substantia nigra in Parkinson's disease by 50-54%, and the zinc content of the caudate nucleus and lateral putamen was also raised by 18-35% (Dexter et al., 1989). Increased levels of copper were found in the pancreas of T2DM patients, and accompanied by a decreased concentration of zinc ions (Wong et al., 2017).

3. Misfolding protein pathologies

Protein molecules fold into secondary structures, which can adopt different conformational states according to physico-chemical parameters of the surrounding environment. Misfolded protein species are prone to forming aggregates, including soluble oligomers and fibrillar amyloid deposits, and can have toxic effects linked with DM and neurodegeneration, and many other pathologies (Hartl, 2017). Protein aggregation is a physiological process regulated by protein proteostasis networks and other factors. These protein control systems tend to decline during aging and increase the risk of MPD development.

In the following, we present proteins involved in AATD, DM, AD, and PD, and discuss how physico-chemical factors influence the mechanism of their aggregation and toxic 'gain-of-function' effects. Moreover, we discuss possible linkages in biochemical pathways between AATD, metal dyshomeostasis and formation of peptide aggregates in DM, AD, and PD.

3.1. α1-antitrypsin deficiency (AATD)

Serpinopathies, in particular Alpha-1-Antitrypsin Deficiency (AATD), are now considered as typical prototypes of misfolding protein disease (Gooptu and Lomas, 2008). The self-assembly event of α1-antitrypsin oligomerization (Carrell and Lomas, 1997) has the same mechanism as the transmissible spongiform encephalopathies and Alzheimer's disease (Dafforn et al., 1999). In addition, polymerization of α1-antitrypsin, like the amyloid protein transthyretin (Kelly, 1996; McCutchen et al., 1993; McCutchen et al., 1995), is enhanced by structure destabilization by extreme pHs and point mutations. Up to now, there is no crystal structure of the pathological α1-antitrypsin polymer, and different models of AAT polymerization have been proposed (Dafforn et al., 1999; Ekeowa et al., 2010).

A healthy person produces approximately 34 mg/ kg of body weight of AAT daily (Llewellyn-Jones et al., 1994). AAT is the most abundant protease inhibitor in the circulation, with around a 5-day half-life and a circulation concentration varying between 1.2 to 2 g/L (Dunlea et al., 2018; Karatas and Bouchecareilh, 2020). In a normal healthy individual, the serum concentration of AAT is 0.85–2.50 g/L (Russo et al., 2009). Serum AAT is produced mainly in the liver and increases three to five-fold during acute phases of inflammation and infection following cytokine (interleukins 1 and 6) and tumor necrosis factor (TNF) activation (Dunlea et al., 2018). Low quantities of AAT are also synthesized in lung intestinal epithelial cells, neutrophils, and alveolar macrophages (Carlson et al., 1989; Molmenti et al., 1993; Mornex et al., 1986).

The wild type (WT) of AAT is called PiM (Protease inhibitor, Pi). The family of normal alleles is referred to as M and the normal phenotype is described as MM. Individuals with deficient alleles have plasma AAT levels 35% lower than the average normal value. The Z allele is the most diffused deficient allele, carried by 2 to 3 % of the Caucasian population in the United States, and in 4% of the Northern European Caucasian population (Ekeowa et al., 2010). About 95% of the significant clinical deficiency is caused by the Z variant of the protein (Bazzan et al., 2018; Ekeowa et al., 2010; Gooptu and Lomas, 2008; Stoller and Aboussouan, 2012). Approximately 0.06% of individuals of Northern European descent have severe deficiency of AAT, with plasma levels less than 0.2 g/L.

Nearly 85% of the Z-AAT is removed by ER-associated degradation or aggregates to form polymers, while 15% is secreted in the serum (Ekeowa et al., 2010; Gooptu and Lomas, 2008; Stoller and Aboussouan, 2012). These polymers form inclusion bodies and are retained in the hepatocytes rather than being secreted in the circulation. AAT aggregation has various clinical manifestations differing between individuals, from asymptomatic to fatal liver or lung disease (Hazari et al., 2017). Hepatocyte damage is believed to be caused (both in homozygotes and heterozygotes) by the presence of polymers of misfolding altered protein and different environmental factors, which determine the disease's prevalence and severity (Silverman et al., 2013).

The synthesis and release of AAT by hepatocytes and alveolar macrophages (AMs) are regulated by inflammatory mediators such as lipopolysaccharides and the acute-phase cytokine IL. In addition, the production of AAT is modulated by elastase in a dose- and time-dependent manner (Perlmutter et al., 1988). AAT polymerizes in alveolar macrophages in the lungs of individuals with AATD, but also in smokers with normal AAT levels with or without COPD (Bazzan et al., 2018). Oxidation stimuli increase the synthesis and secretion of AAT by up to 10-fold, and the excess protein aggregates.

All serine protease inhibitors polymerize under high temperature, oxidation, and denaturing conditions (Gooptu and Lomas, 2009). These factors change the morphological structure of AAT, opening the β-sheet A and allowing aggregation. Nevertheless, polymerization is slower in wild-type M than mutant Z-AAT (Bazzan et al., 2018). It is noteworthy that polymerization can occur with a variety of deficiency mutants of α1-antitrypsin (Elliott et al., 1996; Lomas et al., 1993a; Lomas et al., 1995; Lomas et al., 1993b) and in variants of antithrombin (Bruce et al., 1994; Lindo et al., 1995) and C1-inhibitor (Aulak et al., 1993; Eldering et al., 1995) in association with thrombosis and angioedema, respectively.

Peptides containing high numbers of carboxylic acid groups, as well as imidazole nitrogen atoms, have a high affinity for metal ions

(Al-Harthi et al., 2019) and are involved in metal homeostasis in the human body (e.g. transferrin). Indeed, the plasma concentrations in ZZ-AAT individuals are higher for aluminium, iron and zinc, and lower for copper ions than plasma of MM-AAT and MZ-AAT individuals (Ghio et al., 2013). Moreover, AAT was shown to be involved in iron metabolism, and transferrin levels are correlated with the mean age of onset for people with non-M polymorphism and/or ATT under 1.10 g/L. Kaup et al. (Kaup et al., 2002) showed that AAT-related disturbances in iron, copper, and lipid metabolism may be linked to unnatural metal homeostasis in different tissues, particularly in the brain. Several cases of liver transplantation with double heterozygosity for hemochromatosis, an autosomal recessive disorder characterized by excessive accumulation of iron, and AATD support this possibility (Anand et al., 1983; Lam et al., 2010). In fact, liver biopsies of these clinical cases clearly showed an intra-hepatic presence of both iron and AAT. While the single heterozygous state of these two autosomal recessive diseases is not associated with any accumulation and deposition of these two elements, it is plausible that the presence of AAT may exacerbate a progressive iron overload, and vice versa.

Although the number of potential metal binding sites in AAT (Fig. 1) is comparable to the number in albumin, a known metal chelator and transporter (Al-Harthi et al., 2019), the exact mechanism of metal coordination and homeostasis by AAT remains unknown and needs further elucidation.

3.2. Type 2 Diabetes mellitus

In the physiological state, insulin and glucagon are the two main enzymes that regulate blood glucose levels (Röder et al., 2016). Insulin helps the cells to absorb blood glucose, and when blood glucose levels drop, glucagon triggers the release of stored glucose from the liver into the blood circulation (Röder et al., 2016). In addition, other enzymes and hormones are involved in this complex metabolic process. Particularly amylin (Fig. 2), which is co-secreted with insulin by pancreatic beta cells, but is also synthesized in trigeminal ganglion, dorsal root ganglia, the spinal trigeminal tract, and perivascular fibrils (Kong et al., 1998; Vella et al., 2002). In the state of insulin resistance, islet amyloid polypeptide (IAPP) is overexpressed and prone to aggregate intra- and extracellularly (Gurlo et al., 2010). Small soluble amyloid aggregates, and large insoluble amyloid fibrils of IAPP peptides have been pathologically associated with the death of β-cells, while amylin aggregates were found deposited in the islets of Langerhans in more than 90% of patients with T2DM (Betsholtz et al., 1989; Clark et al., 1988; Johnson et al., 1989; Jurgens et al., 2011; Westermark, 1972). Nevertheless, the etiology and toxic mechanisms of IAPP aggregation are unknown.

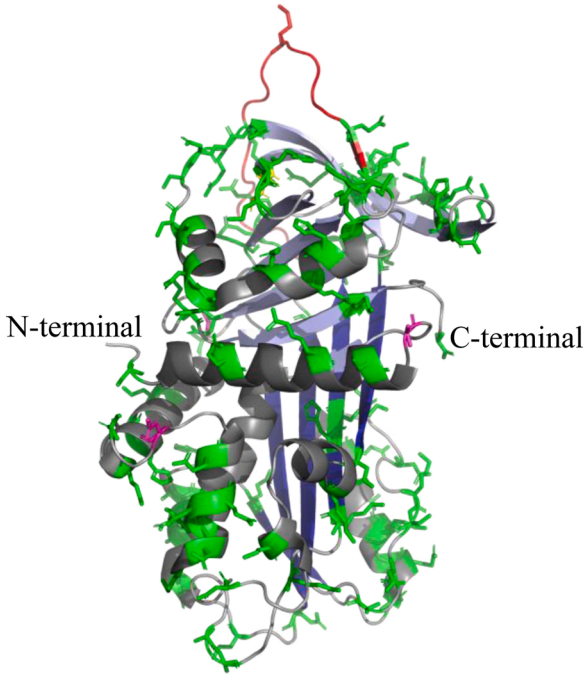


Fig. 1. Crystal structure of human α1-antitrypsin (PDB: 6I7U). AAT is composed of 394 amino acid residues. The glycosylated residues, Asn46, Asn83 and Asn247, are in magenta. The reactive center loop (RCL) is red, as well as Met358 and Glu342. The tertiary structure of AAT consists of nine α-helices (dark grey) and two 3/10 helices (107 residues comprising 26% of the total structure; helices are named A to I), 3 β-pleated sheets (blue) (16 strands made of 115 residues comprising 28% of the total structure; sheets are named A to C). Amino acids with possible metal-binding side chains are indicated in green. Cysteine residues are yellow.

Among protein misfolding disorders, membrane permeabilization, mitochondrial damage and ER stress are suggested to be common mechanisms (Mukherjee et al., 2015). Impaired protein degradation systems (ubiquitin proteasome system (UPS), autophagy and aggresome formation) contribute to the formation of insoluble aggregates. Recently, it was shown that high IAPP expression downregulates Ubiquitin carboxy-terminal hydrolase L1 (UCH-L1) expression (Costes et al., 2011) and leads to alterations in autophagy (Masini et al., 2009) and aggresome (Rivera et al., 2011a; Rivera et al., 2014) pathways in islet β-cells from T2D patients.

The amylin clearance mechanism is zinc ion dependent. Two IAPP-degrading enzymes, namely insulin-depredating enzyme (IDE) (Bennett et al., 2000) and neprilysin (NEP) (Guan et al., 2012; Zraika et al., 2010), are zinc-containing metalloproteases. Importantly, IDE (Leissring et al., 2003) and NEP (Leissring et al., 2003) are also involved in the clearance of protein aggregates in the central nervous system (CNS).

Amylin chemical and structural properties are influenced by pH (Jha et al., 2014) and interactions with metal ions (Abdelrahman et al., 2020; Poulson et al., 2020). The coordination mode and the effects on IAPP structure by interaction with seven metal ions, zinc, copper, iron, nickel, gold, ruthenium, and vanadium were discussed in our recent review (Abdelrahman et al., 2020). The interaction of amylin with metal ions, as well as variable pH conditions, lead to misfolding, and successive formation of protofibrils and mature fibrils.

Various biochemical studies have shown that the amino acid sequence of hIAPP is responsible for the aggregation properties, specifically the ^{22}NFGAILS^{28} region, which plays a key role in amyloid formation (Alghrably et al., 2019; Ashburn et al., 1992; Goldsbury et al., 2000; Jaikaran et al., 2001). Noteworthily, species expressing an aggregation-prone sequence (e.g. humans and cats) also develop T2D spontaneously. Thus, different modifications in the amino acid sequence have been introduced in order to study their effect on aggregation (Khemtémourian et al., 2010; Rahimi and Bitan, 2012; Rozniakowski et al., 2020; Shim et al., 2009; Tofoleanu et al., 2018). However, until now, there has been only one hIAPP polymorphism associated with DM (Meier et al., 2016) (Table 1).

The conformational changes of amylin from monomers to α-helical oligomers and insoluble β-sheet fibrils occurs under pathological conditions (Cho et al., 2008; Clark and Nilsson, 2004; Trikha and Jeremic, 2011). Several studies suggest that the main cytotoxic species are the oligomers rather than the mature fibrils (Cho et al., 2009; Domanov and Kinnunen, 2008; Haataja et al., 2008). The morphology and the structural characteristics of amylin aggregates along with the mechanism of aggregation have been extensively described by Kapurniotu in 2001 (Kapurniotu, 2001), while a more recent review by Ahmad et, al. focused on the structural features of amylin and the mechanisms of its aggregation (Ahmad et al., 2011).

The brain does not synthesize amylin. Nevertheless, amylin aggregates in the cerebrovascular system and gray matter, and leads to impairment of the microvasculature and tissue structure. Moreover, amylin amyloid was found in the walls of cerebral blood vessels where it was linked to the etiology of AD (Djajadikerta et al., 2020). It is likely

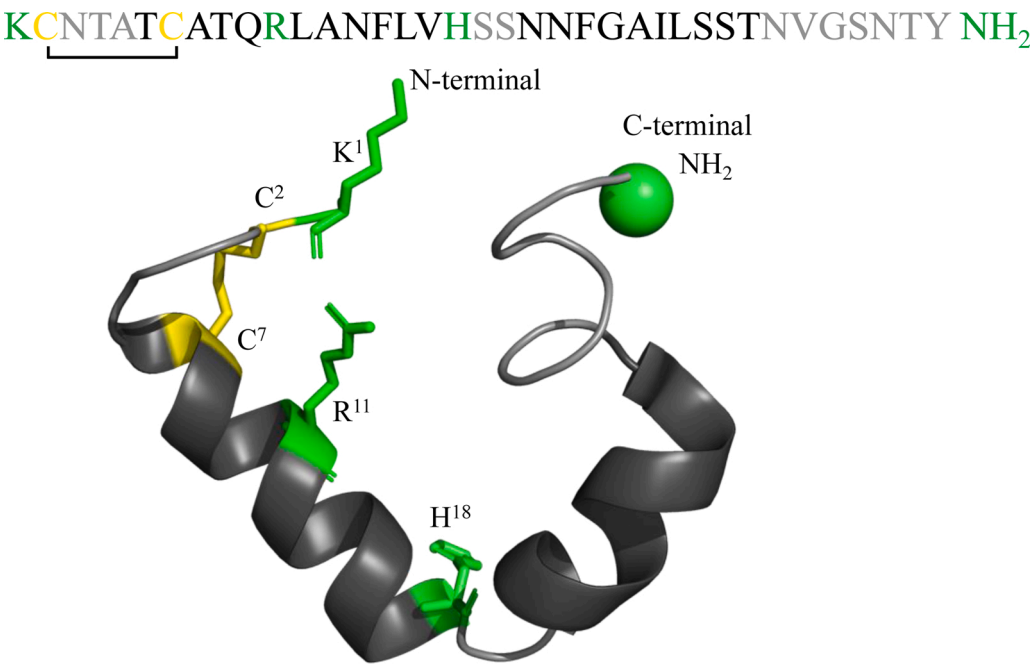


Fig. 2. NMR structure of hIAPP (PDB: 2L86) with the side chains of Cys-2 and Cys-7 shown in yellow to illustrate the disulfide bond. Amino acids with possible metal-binding side chains are labeled green.

that amylin accesses the brain through the Blood Brain Barrier (BBB), and different amylin binding sites are found in cerebral regions (Banks et al., 1995). Toxic amylin oligomers lead to calcium homeostasis dysfunction in astrocytes and neurons, and increase free fatty acid levels in plasma by stimulating lipolysis (Westermark et al., 2011). In a recent review, Bharadwaj et al. (Bharadwaj et al., 2017) connected epidemiological, cognitive, and neuropathological data of T2D with neurodegenerative events. Moreover, they discussed T2D events that promote amyloid beta (Aβ) and tau-mediated neurodegeneration, the role of amylin in the neurodegenerative process, and the role of Aβ and tau in peripheral insulin resistance in T2D.

Recent studies showed that PD patients had lower fasting plasma insulin and increased fasting plasma amylin (Sánchez-Gómez et al., 2020). In vitro studies indicated that amylin accelerates the formation of alpha-synuclein amyloid, but not the contrary, suggesting a one-direction link between T2D and PD (Horvath and Wittung-Stafshede, 2016). Moreover, cytoplasmic phosphorylated α-synuclein deposits were found in the pancreatic β cells of subjects with Parkinson's disease (Martinez-Valbuena et al., 2018).

3.3. Neurodegeneration

Neurological disorders are health disorders in which the functionality of the nervous system gradually declines during disease progression. This heterogeneous group of health perturbations has different characteristics with respect to their symptoms, biochemistry, and the impairment of different parts of the nervous system, such as the central nervous system or peripheral nervous system (Bondi et al., 2017). The most abundant neurodegenerative diseases among the human population are largely age-related Alzheimer's and Parkinson's diseases (Poewe et al., 2017) that are characterized by the presence of amyloids in the brain. The peptide and essential-metal composition of the amyloids varies, and each pathology has prevalence of specific proteins. Serine protease inhibitors are localized in neurofibrillary tangles and senile plaques of Alzheimer's disease patients (Gollin et al., 1992). Recent studies showed that AAT is overexpressed in the brain and the cerebrospinal fluid (CSF) of Alzheimer's (Nielsen et al., 2007; Puchades et al., 2003), Parkinson's (Halbgebauer et al., 2016; Jesse et al., 2012) and Creutzfeldt–Jakob (Abu-Rumeileh et al., 2020) disease patients showing abnormal patterns of its charge isoforms (Abu-Rumeileh et al., 2020). In addition, amylin oligomers and plaques form in the temporal lobe gray matter, blood vessels, and perivascular spaces of diabetic patients. Such amylin aggregates are also present in blood vessels and brain parenchyma of AD patients with diabetes, although amylin and Aβ accumulate independently (Jackson et al., 2013). The basic characteristics of aggregation-prone proteins/peptides involved in AATD, DM, AD and PD are summarized in Table 1.

3.3.0.1. *Alzheimer's Disease (AD)*

Alzheimer's disease (AD) is the most common types of dementia, which is a syndrome of loss or decline in memory and other mental abilities affecting the elderly. AD is characterized by the formation of two main protein aggregates: senile plaques and neurofibrillary tangles, resulting in the progressive degeneration and/or death of neurons. The senile plaques are generated by a deposition in the human brain of fibrils of the β-amyloid peptide (Aβ; Fig. 3A), a fragment derived from proteolytic processing of the amyloid precursor protein (APP), while the tau protein is the major component of paired helical filaments (PHFs), which form a compact filamentous network described as neurofibrillary tangles (NFTs).

Tau in solution does not fold into a well-defined structure but populates a dynamic ensemble of multiple conformations (Daly et al., 2000; Eliezer et al., 2005; Mukrasch et al., 2009; Sibille et al., 2012; Smet et al., 2004). This protein has a unique stability at relatively high temperatures and low pH values. Only five types of residues (G, K, P, S, T) make up half of the sequence. This explains the exceptional solubility and the unfolded nature of the protein but renders the mechanism at the basis of its abnormal aggregation even more mysterious. At first glance, there are no elements in the sequence that are particularly amyloidogenic, such as stretches of hydrophobic residues (as in the case of the Aβ peptide) or glutamines (as in the poly-Q stretches of Huntingtin), whose interactions across and along peptide strands favour the formation of stable β-sheets (Tycko, 2004). Indeed, the abnormal aggregation of tau protein is driven by a transition from a random coil to β-sheet structure (Fig. 3B).

The up- or down-regulation of site-specific phosphorylation events is

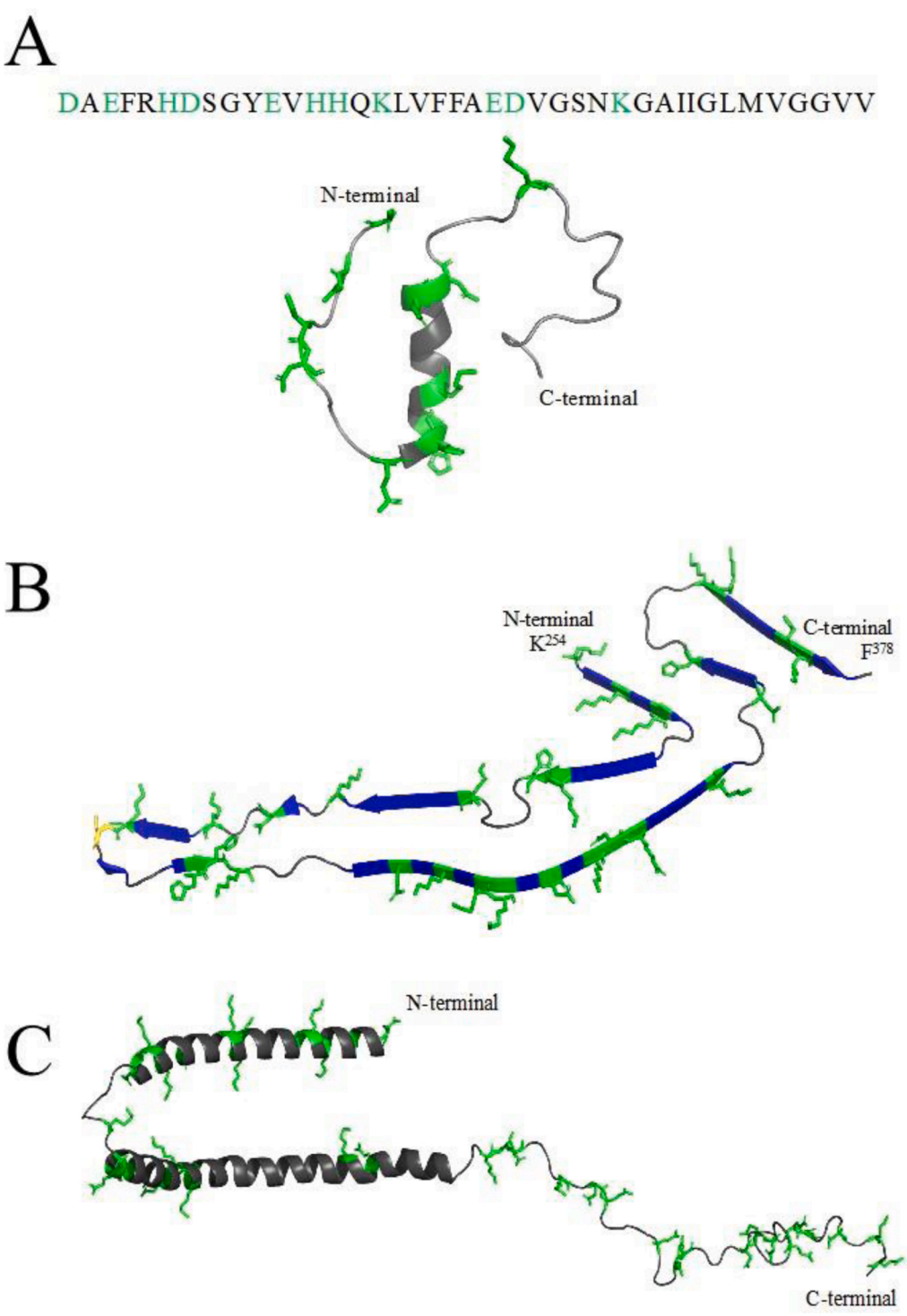


Fig. 3. A) The partially folded structure of human amyloid β (1-40) in aqueous environment (PDB: 2LFM). Amino acids with possible metal-binding side chains are indicated in green. **B)** The structure of the Tau protein fragment (254-378) (PDB: 6GX5) from a narrow pick filament obtained from a Pick's disease brain. Numerous β-sheet secondary structures are colored blue, while amino acids with possible metal-binding side chains are colored in green. Cysteine residues are yellow. **C)** Human α-synuclein structure (PDB: 1XQ8) contains 3 regions characterized by the repetitive consensus sequences KTKEGV, which mediate the physiological tetramerization of α-syn (Dettmer et al., 2015) (essential to avoid aggregation (Schweighauser et al., 2020)). The N-terminal amphipathic region is positively charged (residues 1-60), and essential to regulate membrane interactions, also implicated in α-synucleinopathies (Lashuel et al., 2013). N-terminal acetylation is paramount for producing α-helical oligomers that consequently may have a significant influence on the α-syn effect in PD (Trexler and Rhoades, 2012). The central hydrophobic domain (residues 61-95), recognized as the NAC domain (non-amyloid-β component), moderates protein aggregation by an unknown mechanism (Doherty et al., 2020). The 12-amino acid stretch (residues 71-82), which is absent in β-synuclein, was found to be adequate for α-syn fibrillization (Giasson et al., 2001). The C-terminal region (residues 96-140) is highly enriched with acidic and proline residues and is the main site of phosphorylation. This domain acts in the regulation of nuclear localization and interactions with metals, small molecules, and proteins (Breydo et al., 2012; Lashuel et al., 2013) (Poulson et al., 2020; Schweighauser et al., 2020). Amino acids with possible metal-binding side chains are colored in green.

crucial in the context of both normal cellular function and dysfunction and is known to decrease the tau-microtubules (MTs) interaction. The natively unfolded state of tau shows little tendency for aggregation. In contrast, accumulation of unbound hyperphosphorylated insoluble tau is implicated in a wide range of neurodegenerative diseases known as tauopathies. These include Alzheimer disease (AD), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), agyrophilic grain disease (AGD), Pick disease (PiD), Huntington disease (HD) and frontotemporal dementia with parkinsonism-17 (FTDP-17) (Lee et al., 2001). This phenomenon was correlated with either an imbalance between kinase and phosphatase enzymes (Matsuo et al., 1994), or unknown post-translational modifications such as glycosylation, glycation, prolyl-isomerization, cleavage or truncation, nitration, polyamination, ubiquitination, sumoylation and oxidation (Martin et al., 2011). The DM glucose dyshomeostasis, insulin resistance and impaired insulin signaling favor accumulation of amyloid-β and hyperphosphorylated tau and lead to Alzheimer's disease (AD) development (different possible mechanisms are summarized elsewhere (Farhadi et al., 2019)).

Even if filamentous tau inclusions are a pathological hallmark of tauopathies, increasing evidence suggests that filamentous tau may not be responsible for neuronal dysfunction (Morris et al., 2011). In

particular, filamentous tau inclusions do not correlate with behavioural deficits, and tau-knockout mice do not develop major neurological deficits (Roberson et al., 2007). However, tau reduction has been shown to prevent the behavioural deficits, indicating that unique functions of the protein are fundamental in the pathogenesis of AD, and promoting the potential value of tau-targeted therapies. Nonetheless, these unique gain-of-toxic functions were linked to the presence of soluble tau oligomers (Giacobini and Gold, 2013), which are intermediates of tau filaments closely associated with memory deficits. Addition of small compounds, metals, lipids, and molecular chaperones to either monomeric or fibrillar protein can lead to formation of aggregation intermediates that are usually very stable and characterized as unordered (Barghorn et al., 2005). In most cases, these additive-stabilized oligomers do not seed aggregation of the wild-type protein and are therefore called "off-pathway". Other research (Alonso et al., 1994) indicates that soluble tau aggregates, rather than large insoluble filaments, can play a key role in disease initiation and progression before the development of NFT-induced neurotoxicity. Soluble hyperphosphorylated tau isolated from AD brains has decreased microtubular activity in vitro and sequesters normal tau thereby inflicting the disassembly of microtubules, organelle dysfunctions in neurons, and deterioration of axonal transport, causing apoptosis of neuronal cells (Alonso et al., 1997; Alonso et al., 1996). The oligomeric tau species may also act as seeds for the aggregation of native tau and thus promote the aggregation of neurotoxic tau (Guzmán-Martinez et al., 2013; Lasagna-Reeves et al., 2011).

3.3.0.2. Parkinson's Disease (PD)

Parkinson's disease is the second most common neurodegenerative disorder after Alzheimer's disease (Nussbaum and Ellis, 2003), and is an immense worldwide medical concern. The Global Burden of Disease 2015 analysis show that PD has the highest growth in prevalence and mortality when compared to other neurological disorders (Dorsey et al., 2018b; Feigin et al., 2017). PD is characterized by heterogeneous clinical features including motor symptoms caused by the loss of dopaminergic neurons in the substantia nigra compacta and the loss of neural circuits in the striatum (Subhramanyam et al., 2019), such as akinesia, muscle rigidity, resting tremor, gait disorders and postural instability. During the development of PD, non-motor symptoms (i.e., neuropsychiatric symptoms, pain, and sleep dysfunction) appear at an early stage due to spreading of α-syn aggregates in the brain (Draoui et al., 2020; Faivre et al., 2019; Tysnes and Storstein, 2017).

Neuropathological exams of deep postmortem human brain in Parkinson's disease have revealed the existence of pathological inclusions containing the principally aggregated protein, α-synuclein (α-syn; Fig. 3C). These protein inclusions, a hallmark of the illness, are intraneuronal abnormal accumulation principally of misfolded and aggregated α-syn, and are named Lewy bodies (Breydo et al., 2012). These inclusions are most abundant in the substantial nigra and can even be found in cerebral cortical, monoaminergic and other neurons, where α-syn accumulation, pathologically formed in neurites (Lewy neurites), are associated with PD (Ross and Poirier, 2004). Lewy bodies and Lewy neurites are also related to other neurodegenerative illnesses such as multiple system atrophy and Lewy body dementia. Moreover, Lewy neurites are observed before the appearance of Lewy bodies, which is why the effect of Lewy bodies on neurotoxicity in later phases of PD may be more important (Rocha et al., 2018).

The formation of protein aggregates that represent the key drivers of Parkinson's disease involves complex and entangled interactions at different functional levels that leads to neurotoxicity and causes neuronal death. Several reports have suggested that the major player is α-syn principally by misfolding and aggregation (Guerrero et al., 2013). The levels of α-syn in the central nervous system is dependent on the equilibrium between synthesis, aggregation, and clearance (Lashuel et al., 2013). In fact, the homeostasis of α-syn is preserved by intracellular pathways such as the lysosomal autophagy system and the ubiquitin-proteasome system (Han et al., 2020). The dysfunction of these mechanisms may lead to α-syn-mediated neurotoxicity.

Neurons are particularly sensitive to protein toxicity and vulnerable to autophagy disruption since they do not divide and so are incapable of diluting aggregated protein (Park et al., 2020). Several genetic knockout studies showed that mutations in autophagy-related genes (ATG) and defects in the autophagic process are associated with Parkinson's disease (Bredesen et al., 2006; Sato et al., 2018). In an aged mouse model, Sato et al. showed that ATG7-knockout leads to dopamine neuron loss and motor dysfunction as a result of the increasing formation of inclusions consisting of α-syn and p62, the autophagy adaptor protein, with age (Sato et al., 2018). Autophagy inactivation leads to disruption of the ubiquitin-proteasome system (UPS). In fact, the increase in the accumulation of proteins and p62 affect many pathways including the delay of ubiquitinated protein transfer to the proteasome, inactivation of p97/NCP, the UPS regulator, and accumulation of inactive proteasome subunits that inhibit proteasome degradation (Shin et al., 2020).

Membrane permeabilization by pore formation and endoplasmic reticulum stress is also induced by the accumulation of α-syn oligomers (Zhang et al., 2019). Moreover, a key role for mitochondrial dysfunction in the progression of PD was widely reported through the disruption in mitochondrial dynamics, complex I inhibition of the electron transport chain, and increased reactive oxygen species, in both sporadic and familial PD (Rocha et al., 2018). Di Maio et al. reported that oligomeric and dopamine-modified α-syn binds to the mitochondrial receptor TOM20 and provokes the disruption of mitochondrial protein import mechanisms, and thus the reduction of respiration and increase in reactive oxygen species (ROS) production (Di Maio et al., 2016). Furthermore, new evidence presented by Furlong et al. showed that combining α-syn overexpression and PINK1 deletion causes mitochondrial fission and Golgi fragmentation in neurons (Furlong et al., 2020).

The neuronal death in PD is also associated with high levels of intracellular Ca^{2+} ions, which depolarize mitochondria, provoke ROS formation, and inhibit the function of complex I of the electron transport chain (Panchal and Tiwari, 2019). ROS augmentation leads to an increase in carbonylation of α-syn that enhances their oligomerization and aggregation, and also induces neuronal death by increasing the peroxidation of lipids and degradation of DNA and protein in the substantia nigra (Panchal and Tiwari, 2019).

Neuroinflammation is a central feature of PD pathophysiology. The role of α-syn in stimulating the immune response was underlined by the direct activation of microglial cells in order to consume α-syn (Balestrino and Schapira, 2020). Evidently, the postmortem analyses in the substantia nigra (SNpc) of PD patients showed, in addition to neuronal cell death, activation of microglial cells indicated by the expression of HLA-DR, which is an MHC class II cell surface receptor (Subhramanyam et al., 2019). Moreover, glial cells can be activated by the release of α-syn aggregates from damaged dopaminergic neurons and stimulate the release of pro-inflammatory molecules such as TNFα, IL-6, NOS2, COX2 and ROS in the SNpc contributing to neuronal death by additional microglia exacerbation (Marchetti et al., 2020).

At first glance, the proteins and peptides involved in misfolding protein diseases (Table 1) have no common features. They are encoded by different genes and are expressed in distinct tissues. Moreover, they have different functions, amino acid sequences, and secondary and tertiary structures. Nevertheless, a keen observer will notice numerous amino acids with metal binding sites (Al-Harthi et al., 2019) (carboxylic and amine/nitrogen residues in side chains; namely His, Trp, Glu, Asp, Lys, Arg) that not only can coordinate metal ions, but give the entire protein/peptide an isoelectric point (pI) much distinct from physiological pH. Even a slight variation in the pH environment (e.g., due to the presence of metal ions, high pCO_2) will deviate the charge of these molecules and influence their structure and reactivity in biochemical processes.

The protein aggregation process is also influenced by the pattern of post-translational modifications (Table 1) and the protein clearance mechanism. Both processes are metal-dependent, and any metal

dyshomeostasis leads to significant perturbations in their performance. Targeting metals and the proteosome are two strategies that are currently under pharmacological investigation to cure misfolding protein pathologies.

4. Therapy in misfolding-protein diseases

Metal ions have long been thought to be involved in amyloid aggregation by metal-complex formation and successive formation of insoluble aggregates. Nevertheless, chelating agents that remove metal overload from the cell have proven to be only partially effective in the treatment of neurodegeneration (Bolognin et al., 2009; Nuñez and Chana-Cuevas, 2018) and diabetes (Cooper, 2011; Zheng et al., 2008). In light of recent findings, there is also an interplay between metal dyshomeostasis and dysfunction of the protein degradation system (proteases, ubiquitin proteasome system (UPS) and autophagy) occurring in normal aging and in neurodegenerative pathologies (Grasso et al., 2017). Thus, combined therapies of metal chelating agents and drugs enhancing protein degradation processes could be more effective as misfolding-protein treatments.

Pharmacological therapy, which targets protein degradation processes, is well documented in the treatment of misfolding-protein pathologies. These pathologies include AATD, Alzheimer's' and Parkinson's diseases, the likes of which have not been studied as much in T2DM. A prime example of a proteostasis network (PN) modulator is carbamazepine, a known anticonvulsant drug, which can stimulate proteasomal and autophagy pathways to clear intracellular polymers of AAT (Hidvegi et al., 2010). As yet, no autophagic factors involved in AATD liver disease have been identified; nevertheless, administration of the autophagic enhancers, carbamazepine and rapamycin, lead to the reduction of the hepatocellular burden of aggregated protein, inflammation, and hepatic injury. Carbamazepine is currently being tested in stage 2 clinical trials of severe liver disease caused by Alpha-1 Antitrypsin Deficiency (https://clinicaltrials.gov/ct2/show/NCT01379469).

Chemical chaperones such as trimethylamine N-oxide, glycerol, kifunensin (mannosidase I and II inhibitor), or castanospermine (glucosidase inhibitor) can stabilize the folding and/or rescue the trafficking of Z-AAT. Glycerol and 4-phenylbutyric acid (4-PBA) mediate a marked increase in secretion of ATZ in a model cell line system (Burrows et al., 2000). Trimethylamine N-oxide has been shown to stabilize native AAT, while the phenothiazines enhance autophagic degradation of the aggregation-prone protein huntingtin that causes Huntington's disease (Tsvetkov et al., 2010; Zhang et al., 2007b). Of important note, Phenothiazine is known to target the androgen receptor, which generally functions to bind zinc ions. Suberoylanilide hydroxamic acid (SAHA) showed lower secretion of Z-AAT in cell line models of AATD by inhibition of the histone deacetylase HDAC7 (Bouchecareilh et al., 2012).

Different PN modulators used in AATD treatment showed effectiveness also in the treatment of other conformational pathologies, and some examples are presented in Table 2. Notably, AD outcomes can be simply ameliorated by plasma exchange (Table 2). Drugs enhancing endogenous proteostasis were also applied to different age-related pathologies involving misfolding proteins and proteotoxicity (Perlmutter, 2011). For instance, a decrease in autophagy in older people was linked with Alzheimer's disease, cancer, cardiovascular disorders, inflammatory diseases and glucose intolerance/ metabolic syndrome (He et al., 2012).

Magnesium may improve insulin sensitivity (Fang et al., 2016), while calcium regulates insulin and glucagon secretion, and controls blood glucose (Arruda and Hotamisligil, 2015). T1D and T2D patients have impaired calcium absorption from the intestines (Wongdee et al., 2017), which then leads to changes in calcium metabolism, endoplasmic reticulum stress, and further changes in calcium bone content (Xu et al., 2009; Xu et al., 2012), and muscle contraction (Arruda and Hotamisligil, 2015). Maintaining magnesium and calcium homeostasis in tissues and serum helps to better manage diabetes. Recent research on the correlation between molecular chaperones and micronutrients in T1D mice showed that 4-phenylbutyric acid (4-PBA) restores normal renal magnesium levels at 2 weeks and 2 months after chaperone administration was initiated, while muscular calcium levels return to normal after 2 months (Zhou et al., 2019b). In another study, Gadallah et al. (Gadallah et al., 2019) showed that 4-PBA acid and rapamycin activated autophagy and improved diabetic status in high fat diet/streptozotocin-induced type 2 diabetes.

The ubiquitin proteasome system (UPS) is a key proteolytic system that regulates cell signalling pathways and has an important role in muscle health. Moreover, UPS is involved in ER stress, which triggers myocyte apoptosis in the skeletal muscle of diabetic rats (Reddy et al., 2018). 4-PBA acts as an ER stress inhibitor, and prevents diabetic muscle atrophy in rats by modulating the ER stress response and the ubiquitin-proteasome system. In addition, 4-PBA can control myocyte apoptosis and assist in improving muscle health in diabetes (Reddy et al., 2019).

In 2019, Boccardi et al. (Boccardi et al., 2019) reviewed main "antidiabetic" drugs, which could be candidates in the treatment of AD. Hypoglycemic agents (insulin, Sulphonylureas- Glibenclamide, and Glipizide) and anti-hyperglycemic agents (Metformin, Thiazolidinediones- Pioglitazone and Rosiglitazione, DPP-IV inhibitors- Sitagliptin and Lingliptin, GLP-1 analogues- Lixisenatide and Liraglutide; amylin analogues- Pramlintide) improve insulin levels, but also show effects on AD markers (hippocampal Aβ and synaptic plasticity; neuronal apoptosis; total (phosphorylated)tau; nitrosative and oxidative stress; (neuro)inflammation) in numerous experimental and clinical studies. Most of these drugs (Glibenclamide (Rasheed et al., 2008; Zhou et al., 2019a), Glipizide (Chouhan and Chouhan, 2021; Nazim et al., 2017), Metformin (Logie et al., 2012; Tomic et al., 2011), Pioglitazone (Xi et al., 2019), Rosiglitazione (Levina and Lay, 2011; Wu et al., 2013), Sitagliptin (AL-Bratty et al., 2019; Zhou et al., 2018), Lingliptin (AL-Bratty et al., 2019; Korbut et al., 2020), Liraglutide (He et al., 2020)) are known to activate autophagy, and have metal binding sites.

Autophagy dysfunction was found in different neurodegenerative disorders and is a promising target in AD and PD treatment (Frake et al., 2015). Currently, there are mTOR-dependent (mTORC1 is a negative autophagy regulator, and mTORC2 is a positive regulator) and mTOR-independent agents in clinical trials. Rapamycin (an allosteric mTORC1 inhibitor) shows promising therapeutic results in mutant Aβ (Caccamo et al., 2010), tau (Caccamo et al., 2010) and PrP (Cortes et al., 2012; Wang et al., 2012) models. Nowadays, different 'rapalogs' are investigated as potential therapeutics for neurodegeneration, namely temsirolimus (CCI-779), everolimus (RAD001), and ridaforolimus (AP23573). In addition to drugs inhibiting mTOR, molecules (e.g. metformin (Buzzai et al., 2007), widely used in the treatment of T2DM) that stimulate the AMPK pathway can upregulate autophagy. Among mTOR-independent agents, antihypertensive rilmenidine shows clearance of aggregate-prone proteins and improvement in neurodegenerative impairments.

Defective autophagy in PD and other neurodegenerative disorders was recently review in (Djajadikerta et al., 2020). Rapamycin reduces α-syn in vivo and stimulates autophagosome and lysosomal biogenesis. Also, small-molecule enhancers of rapamycin, namely dSMER10, SMER18, and SMER28 were able to induce autophagy clearance in an mTOR-independent manner (Sarkar and Rubinsztein, 2008). In addition, AMPK-dependent autophagy inducers (metformin, nilotinib, corynoxine B) show promising results in in vivo PD models (Djajadikerta et al., 2020).

In a recent review, Kaeberlein et al. (Kaeberlein and Galvan, 2019) listed beneficial effects of Rapamycin in different animal models of neurodegeneration and aging, which in turn launched an appeal for clinical trials in Alzheimer's disease patients. Importantly, in randomized control trial unrolling generally healthy older (aged 70–93 years) volunteers (Kraig et al., 2018) the oral glucose tolerance tests revealed

Table 2
Examples of common treatment therapies for protein-misfolding diseases.

Type of therapy	Drug name	AD	PD	T2DM
Plasma protein	**AAT**	Plasma exchange in AD patients ameliorates outcomes in Alzheimer's disease patients (Boada et al., 2017; Ding and Lei, 2020)	N/D	Administration of clinical-grade human AAT prolongs pancreatic islet allograft survival (Lewis et al., 2005) and shows cytoprotective effects on pancreatic β-cells via an unknown mechanism (Zhang et al., 2007a). Moreover, systemic administration of AAT restores glucose homeostasis in transgenic mice with overexpression of hIAPP in β -cells, which results in glucose intolerance and impaired insulin secretion. Furthermore, AAT treatment also normalizes expression of the genes encoding Pdx1 and MafA, two transcription factors essential for β -cell function and whose expression is regularly altered in pancreatic islets under stress conditions (Rodríguez-Comas et al., 2020).
PN modulator	**Carbamazepine**	Treatment with carbamazepine enhanced Aβ degradation and reduced plaque burden, decreased tau phosphorylation, and improved cognitive function (Schmukler and Pinkas-Kramarski, 2020)	Carbamazepine alleviates the symptoms of Parkinson's disease and is patented as a method for treating Parkinson's disease and/or a parkinsonian syndrome (ANSARI[1] et al., 2010)	N/D
	Rapamycin & 'Rapalogs'	Treatment with rapamycin and/or its derivatives enhanced Aβ degradation and reduced plaque burden, decreased tau tangle levels, ameliorated neuro-inflammation, restored brain vascular and metabolic functions, and improved cognitive function (Schmukler and Pinkas-Kramarski, 2020) Currently in clinical trials are mTOR-dependent (mTORC1 is a negative autophagy regulator, and mTORC2 is a positive regulator) and mTOR-independent agents. Rapamycin (allosteric mTORC1 inhibitor) showed promising therapeutic results in mutant Aβ (Caccamo et al., 2010), tau (Caccamo et al., 2010) and PrP (Cortes et al., 2012; Wang et al., 2012) models. Currently, different 'rapalogs' are being investigated as potential therapeutics for neurodegeneration, namely temsirolimus (CCI-779), everolimus (RAD001), and ridaforolimus (AP23573).	Treatment with rapamycin or its derivatives lowered mutant α-syn levels (Xilouri et al., 2016), lowered toxicity in dopaminergic neurons (Liu et al., 2013), decreased neuron death (Malagelada et al., 2010), and increased motor function (Bai et al., 2015).	Activation of autophagy by rapamycin, which inactivates mTORC1 (a negative regulator of autophagy) inhibits β-cell death induced by overexpression of human amylin (Rivera et al., 2011b)
	Trimethylamine N-oxide (TMAO)	Trimethylamine-N-oxide (TMAO), a metabolite of gut microbiota, has been implicated in the pathogenesis of Alzheimer's disease (AD). Decreased levels of circulating trimethylamine N-oxide alleviated cognitive and pathological deterioration in transgenic mice and could be a potential therapeutic approach for Alzheimer's disease (Vogt et al., 2018). Moreover, TMAO affects Aβ aggregation (Qi et al., 2009).	Gut microbiota-derived metabolite trimethylamine N-oxide as a biomarker in early Parkinson's disease (Chung et al., 2020) is implicated in different stages of the disease and could be a new potential target for therapy (Janeiro et al., 2018).	Diabetes is associated with higher trimethylamine N-oxide plasma levels (Dambrova et al., 2016). TMAO decreases the aggregation rate of hIAPP (Kumari et al., 2020).
	4-phenylbutyric acid (4-PBA)	4-PBA penetrates the blood–brain barrier and exhibits significant neuroprotective effects in mouse models of neurodegenerative diseases, such as Alzheimer's disease (AD) (Ricobaraza et al., 2009; Ricobaraza et al., 2012) and Parkinson's disease (PD) (Inden et al., 2007; Ono et al., 2009). 4-PBA attenuates the pathogenic potency in human α-synuclein A30 P + A53 T transgenic mice (Ono et al., 2009)		4-PBA restored glucose homeostasis in a mouse model of type 2 diabetes (Özcan et al., 2006), and inhibited the process and development of diabetic nephropathy in rats (Luo et al., 2010)
	Phenotiazines	Phenotiazines selectively inhibit Alzheimer's disease-like tau aggregation (Wischik et al., 1996). Methylene blue (MB) slowed down progression of AD (Oz et al., 2009) and PD (Varga et al., 2017)		Chlorpromazine was used in the treatment of psychotic disturbances. About every fourth patient who had been treated for one year or longer with more than 100 mg daily of chlorpromazine or corresponding doses of another psychoactive phenothiazine developed hyperglycaemia and glycosuria. In 25 percent of the patients, remission occurred either after withdrawal of the drug or reduction in dosage (Thonnard-Neumann, 1968).
	Metformin	Metformin therapy reduced levels of Aβ, decreased tau phosphorylation and improved cognitive functions (Schmukler and Pinkas-Kramarski, 2020).	Metformin therapy led to lower mutant α-syn levels (Bai et al., 2015), reduced mitochondrial pathology, and increased motor function (Pérez-Revuelta et al., 2014)	Metformin is a first-line treatment in T2DM. It has been linked to different side effects, particularly to renal complications in diabetic patients (Lalau et al., 2015) Metformin is a known metal chelator, with high stability of copper complexes (Abu-El-Wafa et al., 1987; ANSARI[1] et al., 2010).
	Suberoylanilide hydroxamic acid (SAHA)	Suberoylanilide hydroxamic acid protects dopaminergic neurons from neurotoxin-induced damage (Chen et al., 2012a)		N/D

no rapamycin-induced change in blood glucose concentration, insulin secretion, and insulin sensitivity, suggesting that rapamycin treatment could be used by neurodegenerative patients with diabetes.

Last but not least, a new approach based on monoclonal antibodies was experimented in the treatment of AATD. Monoclonal antibodies (mAb4B12) were shown to block Z-AAT polymer formation without compromising its inhibitory activity (Ordóñez et al., 2015). The antibodies treatment could also be a new approach in neurodegeneration. Recently terminated Phase III clinical trials of Aducanumab and Crenezumab in the therapy of Alzheimer's disease give new promises for an effective therapy (Hung and Fu, 2017), but also open up new questions in amyloid hypothesis for the onset of the disease, and only partially explain the complex pathologies.

Despite promising results, all the latest strategies require further clinical studies and experiments in cell and animal models. The development of new therapies for AATD represent a real promise to develop effective strategies and agents that block the formation of protein aggregates or stimulate pathways that accelerate their clearance (Lomas, 2018) not only in AATD but also in other conformational diseases.

5. Conclusions

Misfolding protein pathologies are clearly linked to the dysfunction of essential and toxic metal ion homeostasis. Peptides involved in conformational diseases have numerous metal binding sites, but it is unclear whether formation of metal complexes, and their insoluble aggregates, is a cause of the pathology or an adaptive mechanism and/or consequence of metal overload due to environmental factors.

Alpha-1 antitrypsin is an abundant protein in human blood, and is seemingly involved in essential-metal ion homeostasis. Insufficient quantities of circulating AAT lead to dyshomeostasis of essential metal ions (namely iron, copper and zinc), which in turn may result in the development of other misfolding protein diseases (diabetes and neurodegeneration). Fast diagnosis of AAT insufficiency, by simple blood analysis, followed by the proper therapy could prevent development of diabetes and onset of neurodegeneration.

The correlation between low AAT serum levels, essential metal dyshomeostasis and protein misfolding pathologies, as presented in this review, could lead to new therapeutic strategies in the clinical practice of diabetes and neurodegenerative disorders. Diabetic and neurodegenerative disorders could be indications for the serum AAT quantitative analysis. Patients with low AAT levels should undergo genotype analysis for AAT mutations and quantitative analysis of essential metal ions in whole blood and serum. In order to diagnose the risk of diabetes and neurodegeneration early on, these non-invasive analyses should be prepared in childhood, with particular attention to subjects with familiarity to the misfolding protein pathologies. The diagnosis of contemporary low AAT levels and essential metal ions dyshomeostasis could be followed by the therapy with the AAT extracted form serum of healthy humans, which is currently used in the treatment of AATD. The restoration of normal metal homeostasis in the treatment with AAT, as well as potential amelioration of diabetic and neurodegenerative conditions, has never been investigated and creates an urgent need for future studies.

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