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The incorrect folding of proteins and their involvement with pathological processes

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ABSTRACT
During synthesis and the period in which they exert their cellular function, there is monitoring so that the proteins maintain a certain three-dimensional folding, where their energy levels are stabilized and their biological activity is maintained. Changes in cellular conditions can modify this structure, favoring its aggregation into insoluble complexes, called amyloidosis, depositing in the intra or extracellular environment. Recent data indicate that several types of proteins are involved in some type of amyloidosis, presenting a systemic character, or depositing in a specific tissue. The classification used for these cases considers the amyloid source, the pathology, and the organ affected. Protein fragments derived from immunoglobulin light and heavy chains are responsible for primary systemic amyloidosis. In secondary amyloidosis, there is the participation of circulating plasma protein, acting in inflammatory processes in different organs. Dialysis-related amyloidosis, on the other hand, is characterized by damage to bone tissues and joints in patients with chronic kidney disease. Most studies related to localized amyloidosis involve neurodegenerative diseases such as Alzheimer's and Parkinson's diseases. These heterogeneous pathologies associated with the incorrect folding of proteins are subject to genetic influence, which is increasingly evidenced, despite their multifactorial character. Deficiencies in the cellular proteostasis processes, i.e., in the surveillance that confers the quality control of these proteins, leading to their recovery or sending them for recycling, tend to increase with age. For this reason, most of the time these amyloidoses are related to the individual's aging processes.

Keywords: Protein aggregates, Proteostasis, Chaperone, Proteosome.

1 INTRODUCTION

1.1 PROTEIN STRUCTURE

Proteins are macromolecules that perform several important functions in all living beings, being fundamental structural components, as well as participating in dynamic functional activities, both intra and extracellular. To perform their function, proteins, which are made up of long polypeptide chains, need to be coiled together into a regular functional three-dimensional structure. The folding of these

chains has a multidimensional nature, where different configurations can be defined by the minimum state of free energy of Gibbs, that is, the proteins fold in such a way as to decrease the free energy, reaching their functional native form (PANAHI, 2019). During their existence, proteins can adopt different conformational states in the environment, from their synthesis in ribosomes, through post-translational modifications in specialized cellular compartments, acquiring a functional native architecture, to their destruction for recycling by proteases, when they lose their original shape and, therefore, no longer have a biological function. In terms of three-dimensional structuring, the configurations presented by these biopolymers involve a highly complex equilibrium, defined thermodynamically and kinetically by their primary sequence (number and composition of amino acids) and by specialized tutor enzymes that direct these interactions (chaperones). When native structural characteristics are not maintained, complexes responsible for final quality control eliminate non-functional protein forms. Although the primary level of these proteins has co-evolved according to the type of environment in which they act in their soluble states, certain conditions can alter protein configurations, converting them into non-functional insoluble aggregates that are potentially harmful to the environment where they are deposited (CHITI; DOBSON, 2017).

1.2 PROTEIN AGGREGATES

Amyloidosis is a pathology associated with the deposition of protein fibrils found in several vertebrate species. The incorrect folding of excess proteins can potentially be related to pathologies by several mechanisms, including loss of biological function, gain of toxic function or by the entrapment of other misfolded proteins, disfavoring their recovery or recycling. The agglomeration of these proteins with a secondary β-pleated, cross-the-leaf configuration and insoluble is an intrinsic feature of amyloid diseases (KARUNARATHNE, *et al.* 2023).

The name amyloid means similar to starch (Greek: amylon or Latin: amylun), and was used for the first time in 1854 by Rudolf Virchow to define regions of tissues that presented a histological stain similar to starch, when stained with the mixture of iodine-sulfuric acid (KYLE, 2001). The development of more well-defined methodologies, using dyes such as Congo red and polarization microscopy, showed that these observed extracellular deposits were not starch, a reserve polysaccharide found in vegetables, but rather proteins. Based on this finding, it was observed that these deposits could occur in several different tissues and organs, and that in many cases they are associated with specific pathologies (BENSON, *et al.* 2019).

Amyloid formation involves a series of protein aggregation events, leading to the generation of mature insoluble fibrils that accumulate in different types of tissues in the body. In addition to the formation of insoluble fibrils, soluble oligomeric species can also be generated, which constitute the most cytotoxic molecular forms produced during the amyloid cascade. The direct or indirect action of

these soluble oligomers seems to be involved with cell death, and in some cases with the functional alteration of a given organ (ALMEIDA; BRITO, 2022).

Current data indicate that at least 36 different proteins have already been identified as participants in amyloidogenic processes in humans, with 19 of these proteins being deposited in some specific organ (localized amyloidosis), at least 14 types of proteins and their variant forms appear to be distributed throughout various parts of the body (systemic amyloidosis), and at least 3 types of proteins can promote localized or systemic deposits. These last three groups involve fragments derived from the light chain, heavy chain of immunoglobulin and β2 microglobulin, a protein present in almost all cells and found in the blood in some types of cancer (PICKEN, 2020; PEDRO, *et al.* 2019, BENSON, et al. *2019, MUCHTAR,* et al. 2021).

Early studies linked these protein deposits to neurodegenerative disorders, such as Alzheimer's, Parkinson's and spongiform encephalopathy. However, it was found that extracerebral amyloidosis is also important, since its incidence is relatively common in processes involving cellular and individual aging. Virtually all elderly humans have amyloid deposits at some point, and they are often associated with the cardiovascular system, and they can also be associated with important chronic diseases, such as type 2 diabetes mellitus and rheumatoid arthritis (WESTERMARK, 2015).

These protein aggregations present themselves in various ways, being related to processes that lead to heart failure due to ventricular hypertrophy, hepatomegaly, nephrotic syndrome, macroglossia, hypoorthostatic hypotension, ecchymosis, autonomic and peripheral neuropathy, carpal tunnel syndrome, lameness of the mandible and joint deposits. Secondary amyloidosis may involve hepatosplenomegaly, proteinuria, renal failure, and orthostasis. Beta amyloidosis in the nervous system presents as Alzheimer's disease (BHUSHAN, 2021).

The cytotoxicity of these amyloidogenic proteins correlates with their size and external exposure of their hydrophobic sites, which in the native configuration are located inside the protein. Exposure to these hydrophobic nuclei is potentially harmful, as they interact with other nonpolar surfaces in cellular compartments and can interfere with a wide spectrum of biological processes (ARGHAVANI, *et al.* 2022). The mechanism of toxicity is not yet fully understood, but it is possible that the oligomerization of these proteins would play a central role in inducing cell damage. Evidence for this comes from the characterization of these oligomers, since these hydrophobic groups exposed on the surface seem to be a determining factor in interactions with the phospholipid bilayer of cell membranes, binding to different protein receptors and other cellular components. Interactions can result in decreased receptor activity, increased membrane permeability, formation of pore-like structures, altering ionic homeostasis (PANAHI, 2019).

Strategies to combat amyloidogenesis and related toxicity include the use of drugs consisting of small molecules capable of inhibiting amyloid aggregation, or that are capable of stimulating the

degradation of these fibrils by proteosomes and autophagy, or that promote the disaggregation of toxic amyloid fibers or soluble oligomers (CHUANG, *et al,* 2018).

1.3 CHAPERONES

During the production process, chaperones prevent aggregation and promote the efficient folding of proteins by cells, contributing to the maintenance of proteome homeostasis. (ALMEIDA; BRITO, 2022). Chaperones are part of a group of proteins that have their synthesis increased under conditions of cellular stress. Originally known as Heat Shock Proteins (HSP), they promote cellular defense against the formation of amyloid fibrils, employing strategies that prevent the aggregation of the set of cellular proteins, favoring the correct folding and recovery of misfolded proteins from transient interactions. Chaperones prevent the conversion of native proteins into amyloids (WENTINK, *et al* 2019).

When this quality control system is disrupted, the polypeptides proceed to incorrect folding, inactivity, and aggregation. In addition to chaperones, there are other proteins that disaggregate protein tangles at the expense of ATP, showing a co-chaperone activity (DOYLE, *et al*. 2013). Probably several native conformations in the proteins are possible from the activity exerted by the chaperone, and these configurations can lead the same polypeptide chain to present different functions. The chaperone is capable of distinguishing the functional structures of proteins, recognizing and acting on those that are misfolded and neglecting those that have the native configuration (MURONETZ, *et al.* 2022).

Laboratory assays using yeast models have shown that even small changes in the homeostasis of the folding of an amyloidogenic protein can lead to a gain in proteotoxic function and that the cytoprotective function is dependent on the action of chaperones (DOUGLAS, *et al*. 2008). There are also groups of non-protein chaperones, which are small molecules capable of stabilizing the native state or disaggregating the misfolded state of amyloid chains. The chemical chaperones that most participate in protein recovery are hydrophobic compounds, such as bile acids, steroid hormones, and osmolytes such as some carbohydrates, polyols, glycerin, and methylamines (ALMEIDA; BRITO, 2022).

Studies carried out by WYatt et al. showed the role of extracellular chaperones in amyloidosis. In this review article, the authors suggest that these chaperones play a central role in proteostasis, participating in the patrolling of extracellular biological fluids, looking for misfolded proteins, facilitating their clearance via endocytic receptors. The interruption or overload of this extracellular proteostasis would lead to the increase of these amyloidogenic proteins with consequent formation of extracellular aggregates and pathology (WYATT, 2012).

1.4 PROTEOSOME

The ubiquitin-proteosome system (UPS) is a multicatalytic complex of proteases responsible for the renewal of most cellular proteins. They have a ring structure with a narrow pore that selectively degrades target proteins into peptide fragments (TÜRKER, *et al.* 2021). UPS is the main pathway for the degradation of misfolded, unnecessary, or damaged intracellular proteins. When their effectiveness decreases, these proteins aggregate in the medium, which can block normal functions, even leading to cell death. The maintenance of proteostasis is important for neurons, due to their complex architecture and inability to dilute the accumulated load since they no longer enter the process of cell division (THIBAUDEAU, *et al.* 2018).

Experimental results obtained by Chocron and collaborators demonstrated that proteosome dysfunction in animal models is a prominent marker of early stage Alzheimer's disease. Induction of appropriate proteosome assembly was able to reduce protein aggregation in cell culture, drosophila, and transgenic mice. They also observed that proteosome agonists derived from the TAT peptide reduced deficits in animal models of Alzheimer's. The protective effects found showed an increase in the turnover of the Amyloid Precursor Protein and a reduction in the levels of the peptide Aβ42, responsible for this amyloidosis (CHOCRON, *et al.* 2022).

2 TYPES OF AMYLOIDOSIS

Several classification systems have been developed to indicate the different types of amyloidosis, and currently, in medical practice, it is based on the type of protein involved. The recommended nomenclature uses the letter A to name the word amyloid, followed by the abbreviation that defines the protein type. Systemic amyloidosis of the AL (Amyloid derived from the immunoglobulin light chain), AA (Amyloid derived from Apoprotein), ATTR (Amyloid derived from Transthyretin), as well as localized amyloidosis (LARREA, *et al.*, 2015; PICKEN, 2020). They can also be classified according to the etiology presented as systemic, hereditary, central nervous system, ocular or located in certain organs. However, the definitions of the most common types found in the literature are AL, AA, ATTR, and amyloid dialysis-related type β2M (BUSTAMANTE, ZAIDI, 2023, REAL de ASÚA, *et al.* 2014).

The population prevalence of these amyloidosis varies between different regions of the world. In more affluent countries, the primary (AL) and transthyretin (ATTR) types are the most frequent types found in cases of systemic amyloidosis. On the other hand, in resource-limited countries, secondary amyloidosis (AA) is more prevalent. This variation probably results from a higher burden of chronic infectious diseases such as tuberculosis, leprosy, and osteomyelitis as observed in poorer countries and regions (WESTERMARK, *et al*., 2008).

2.1 PRIMARY AMYLOIDOSIS (AL)

AL (or primary) amyloidosis is the most common form of the disease. It starts in the bone marrow, where red and white blood cells are formed. One type of lymphocyte, called a plasma cell, is a producer of immunoglobulin (antibody), a complex defense protein composed of light and heavy chain units. Plasma cells are differentiated B lymphocytes that play a significant role in the humoral adaptive immune response (ALLEN, SHARMA, 2023). Physiologically, plasma cells release complete antibodies, and the body breaks down these proteins and recycles them after a short period. However, in LA, many unassembled and incorrectly bent light chains are generated, which cannot be broken down effectively. They bind together to form amyloid fibrils that accumulate in the extracellular space of organs and tissues, impairing the normal functioning of the body. Manifestations usually arise in the kidney, heart, liver, spleen, nerves, intestines, skin, tongue, and blood vessels (AMYLOIDOSIS SUPPORT GROUP, 2023).

The symptoms of AL amyloidosis are different in each patient, depending on which organ is affected. The most common symptoms are fatigue, weight loss, and bloating. Chronic kidney disease is common in patients with AL amyloidosis, where amyloid deposits in the kidneys affect their way of filtering toxins and proteins from the blood, leading to nephrotic syndrome (AMYLOIDOSIS FOUNDATION, 2023). It is estimated that 75% of patients with AL amyloidosis have proteinuria, often accompanied by edema of the lower limbs (PALLADINI, MERLINI, 2009).

Cardiac involvement is observed in approximately 60% of patients, and these amyloid deposits make the heart muscle thicker and stiffer, typically characterized by thickening of the interventricular septum and ventricular wall, altering its functionality, resulting in fatigue and possible changes in the cardiac electrical system, which can lead to an arrhythmia. (AMYLOIDOSIS FOUNDATION, 2023). Other manifestations that may occur include sudden death or syncope due to arrhythmia or heart block and, rarely, angina or infarction due to amyloid buildup in the coronary arteries.

In approximately one-third of cases of systemic amyloidosis, cardiac clinical manifestations are usually characterized by congestive heart failure due to restrictive cardiomyopathy, cardiomegaly, systolic dysfunction, postural hypotension, and arrhythmias. Gastrointestinal clinical manifestations include obstruction, ulceration, malabsorption, hemorrhage, protein loss, and diarrhea, and may infiltrate the tongue, esophagus, and intestine, causing digestive bleeding (MONTEIRO, DIZ, 2015).

In the nervous system, amyloid deposits can affect the nerves of the hands, feet and legs, causing pain, numbness and tingling, in addition to loss of sensitivity to temperature, called peripheral neuropathy. Nerves that control blood pressure, heart rate, intestinal motility, and other body functions can also be affected, called autonomic neuropathy. (AMYLOIDOSIS FOUNDATION, 2023).

2.2 SECONDARY AMYLOIDOSIS (AA)

Amyloid A (AA or secondary) amyloidosis, also known as serum amyloidosis, arises through an inflammatory disease or chronic infection, resulting from increased levels of circulating amyloid A protein. AA deposits are formed by fragments of the N-terminal portion of the amyloid A acute phase reactant protein, a polymorphic apolipoprotein component of High Density Lipoprotein (LDL) that is stimulated by the inflammatory process, and can reach continuously high plasma concentrations between 100 and 1000 mg/L (OBICI, et al. 2005). Patients who have this condition for six months or more are at risk of AA. These conditions include rheumatic disease, inflammatory bowel disease, tuberculosis, osteomyelitis, lupus, and hereditary fever syndromes, such as familial Mediterranean fever. Amyloid deposition usually begins in the kidneys, but the liver, spleen, lymph nodes, and intestine are also commonly affected. (AMYLOIDOSIS SUPPORT GROUP, 2023). It can lead to multi-organ dysfunction, including alteration in glomerular filtration rate and proteinuria (THORNE, *et al.* 2022). During the inflammatory process, some signaling cytokines are released, such as interleukin 1 (IL-1), interleukin 6 (IL-6), and tumor necrosis factor (TNF), which activate the hepatic synthesis of serum amyloid A, the precursor of AA fibrils. Therefore, effective treatment of the underlying inflammatory disorder blocks the stimulus for precursor synthesis. (XAVIER, 2008).

Nephropathy associated with AA amyloidosis presents as proteinuria and renal failure. The purpose of therapy is to interfere with the production of the precursor protein and prevent the formation of additional fibrils. Decreased production of serum amyloid A protein is associated with improved renal function, stabilization or regression of amyloid deposits. (COSTA, 2010). Management of renal AA amyloidosis is focused on treating the inflammatory condition to stabilize glomerular filtration rate, reduce proteinuria, and slow progression to renal failure (THORNE, *et al.* 2022).

2.3 FAMILIAL AMYLOIDOSIS (HEREDITARY)

Familial (or hereditary) amyloidosis is associated with the mutant transthyretin (TTR) protein produced in the liver. TTR is a protein that helps transport thyroxine (a thyroid hormone) and retinol (vitamin A) around the body. The peripheral nervous system (somatic and autonomic) and heart are the most affected sites, therefore, peripheral sensorimotor neuropathy, dysautonomia, and cardiomyopathy, often in combination, are the common phenotypes (MANGANELLI, *et al*., 2022). Symptoms occur in middle age and old age. When the nerves are initially affected, the clinical picture is known as familial amyloid polyneuropathy; If the heart is affected first, it is called familial amyloid cardiomyopathy. In addition to peripheral and autonomic neuropathy and heart disease, ATTR can lead to vitreous opacity. Familial ATTR is a disease that begins with symptoms of paresthesias of the lower limbs, followed by a progressive deterioration of gait, erectile dysfunction, urinary incontinence and gastrointestinal involvement, with death within 10 years, when treatment is not instituted.

Transthyretin plays a central role in three pathologies characterised by TTR deposition in the form of amyloid: a sporadic disease in which transthyretin is exclusively native (wild-type wt-TTR), systemic senile amyloidosis (SSA) and two familial diseases in which a mutation of the TTR gene occurs, familial amyloid cardiomyopathy (FAC) and familial amyloid polyneuropathy (FAP). (SEIXAS, 2016).

The deposited protein is a mutated form of transthyretin, where more than a hundred different forms have been described. The most common TTR mutation is called Val-30-Met, which causes nerve damage and electrical problems in the heart. (AMYLOIDOSIS SUPPORT GROUP, 2023). These amyloidogenic variants are thermodynamically less stable, resulting in the dissociation of tetramers into monomers, and these units have a greater propensity to aggregate into fibrils (BUSTAMANTE, ZAIDI, 2023).

2.4 DIALYSIS-RELATED AMYLOIDOSIS TYPE β2M

Dialysis-related amyloidosis (ARD) is a debilitating pathology that is characterized by the accumulation and deposition of amyloid fibrils composed of beta2-microglobulin (β2-M) in bone tissues, periarticular structures, and internal organs of individuals who have suffered from chronic kidney disease (CKD) and are approved for dialysis treatment (HEEGGARD, 2009). β2-M is a constituent of the major histocompatibility complex (MHC) of cell membranes that is usually removed through glomerular filtration, followed by reabsorption and catabolism in the proximal tubules. In patients with reduced renal function, β2-M clearance decreased, increasing its plasma flow and gradual deposition in tissues. The most common symptoms related to patients with ARD are shoulder pain related to scapular periarthritis and amyloid rotator cuff infiltration, and symptoms of carpal tunnel syndrome, which is a very common manifestation in these patients (ZEGRI-REIRIZ, *et al,* 2019, DONNELLY, *et al.* 2019).

Table 1 - Classification of amyloidosis, source from which the protein is derived, and which organs are affected by amyloid deposition.

Category	Source of amyloid	Syndrome	Affected organs
Primary amyloidosis, AL	Plasma cells in the bone marrow (immunoglobulin light or heavy chains).	Primary or associated myeloma.	Kidneys, heart, liver, spleen, nerves, gastrointestinal tract, skin, tongue, and blood vessels.
Secondary amyloidosis, AA, or serum amyloidosis	Circulating inflammatory protein (Serum amyloid A).	Reactive, secondary to chronic inflammation or infections.	Kidneys, liver, spleen, lymph nodes, and intestine.
Familial amyloidosis, ATTR	A mutant, wild-type protein formed in the liver.	Hereditary and senile.	Heart, which can cause familial amyloid cardiomyopathy and familial amyloid polyneuropathy
Dialysis-related amyloidosis, DRA	Circulating serum protein, β2-M.	Associated with dialysis.	Bone tissues, periarticular structures, and internal organs of individuals who have

			suffered from chronic kidney disease.

3 FINAL CONSIDERATIONS

Amyloidosis consists of a rare and heterogeneous group of alterations characterized by misfolded proteins, where groups of nonpolar amino acids are exposed, favoring the association of these components in insoluble aggregates, deposited in the intra or extracellular environment, leading to organ damage. Many of these amyloidosis are related to the individual's aging processes, and literature review studies have indicated the participation of more than 10 different types of proteins involved (PICKEN, M.M., 2020). Among the most studied proteins, amyloid beta (Aβ42), alpha synuclein, transthyretin, islet amyloid polypeptide, atrial natriuretic factor, and fibulin-like matrix protein are among the most studied proteins. Most studies have always focused on neuronal amyloidosis (TASAKI, M *et al.* 2021). Although the aging process is related to amyloid deposits, studies reveal that cognitive aging, in general, is a multifactorial process (PRASAD, K. 2019).

Cellular proteostasis involves the quality control of the newly synthesized protein and those active proteins that act to perform their function. Autophagy, mediated or not by chaperones, is a surveillance process that contributes to the quality control and recycling of these denatured proteins. The decrease in surveillance capacity is proportionally associated with increasing age and, consequently, with the incidence of neurodegenerative diseases, such as Alzheimer's and Parkinson's disease, associated with the accumulation of protein aggregates in the brain in these patients (BOURDENX, M, *et al*. 2021).

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