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Transthyretin: Molecular Functions, Immunological Roles and Its Involvement in Amyloidogenesis

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Abstract Transthyretin (TTR) is a homotetrameric transport protein primarily synthesized in the liver and choroid plexus. It serves as a carrier for thyroxine and retinol-binding protein but also exhibits broader biological functions, including neuroprotection and proteolytic activity. TTR also regulates myeloid cell development to regulate immune cell reaction. Structural destabilization of TTR can lead to its misfolding and aggregation into insoluble amyloid fibrils, resulting in transthyretin amyloidosis (ATTR), a group of systemic disorders characterized by extracellular amyloid deposition in multiple organs. Two major forms of ATTR have been described: hereditary (variant, ATTRv) and wild-type (ATTRwt) amyloidosis. ATTRwt arises from the aggregation of non-mutant TTR, primarily causing cardiomyopathy, whereas ATTRv results from pathogenic TTR gene mutations associated with neuropathic, cardiac or mixed phenotypes. Although current therapies can stabilize TTR tetramers or facilitate amyloid clearance, they primarily manage disease progression rather than achieve cure. This review aims to integrate current knowledge on the molecular structure and physiological functions of TTR, its immunomodulatory and cell-protective roles and its pathological involvement in amyloidogenesis. By highlighting the intersection between TTR's biological and immunological functions, the review underscores its relevance in understanding disease mechanisms and developing targeted therapeutic strategies.

Key Words Transthyretin, Thyroxine, Polyneuropathy, Amyloidogenesis

INTRODUCTION

Transthyretin (TTR), also known as prealbumin, is a 55 kDa homotetrameric protein widely distributed in plasma and cerebrospinal fluid (CSF). Each TTR monomer consists of 127 amino acid residues and four identical subunits assemble to form the tetrameric structure that is rich in β-sheets. TTR serves primarily as a carrier of thyroxine (T4) and retinol by forming a complex with retinol-binding protein (RBP), thereby facilitating their transport to various tissues, including the brain [1]. The TTR gene, spanning approximately 7 kb with four exons and three introns, is located on **chromosome 18q11.2-q12.1 [1]. The liver is the main site of TTR synthesis, secreting it into the bloodstream at physiological concentrations of 0.2-0.4 mg/ml with a half-life of about two days. Additionally, the choroid plexus produces TTR that is secreted into CSF at concentrations ranging from 0.02 to 0.04 mg/ml, while smaller amounts are also expressed in the intestine, heart, skeletal muscle and spleen [2].

Beyond its transport functions, TTR exhibits neuroprotective and regulatory roles. Experimental studies have demonstrated that TTR can reduce the formation of amyloid-β aggregates in the brain, thus exerting a protective effect against neurodegenerative processes [1]. However, under certain pathological conditions, conformational alterations in TTR destabilize its tetrameric structure, leading to monomer misfolding, aggregation and formation of insoluble amyloid fibrils** that accumulate in extracellular tissues [3]. These amyloid deposits are implicated in a spectrum of TTR-related amyloidoses, including hereditary transthyretin (ATTRv) amyloidosis, **senile systemic amyloidosis, familial amyloid cardiomyopathy and neuronal amyloidosis [4-8].

Recent evidence suggests that inflammatory and immune-mediated processes play an essential role in the pathophysiology of TTR amyloidosis [5]. Misfolded TTR can interact with the receptor for advanced glycation end products (RAGE), leading to activation of inflammatory signalling pathways and the release of cytokines such as interleukin-6 (IL-6) and interferon-γ (IFN-γ) [5]. These responses may contribute to tissue damage and disease progression, linking protein misfolding to immune dysregulation.

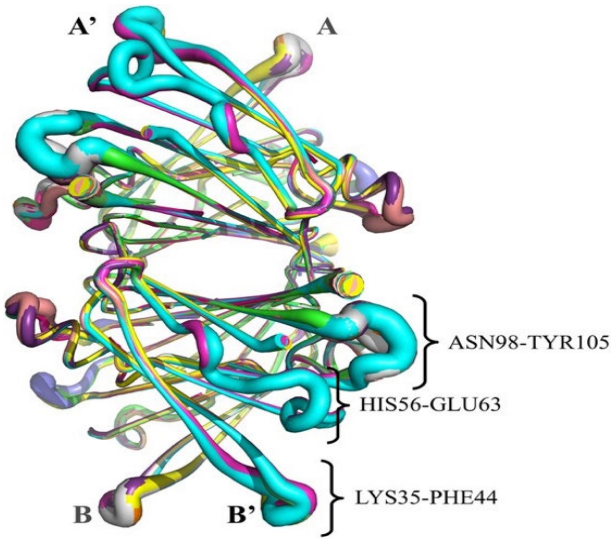

Figure 1: TTR tetramer-ligand complexes. The variable-width corresponds to values of experimental B-factors. The segments of sequence with larger flexibilities are also indicated [11]

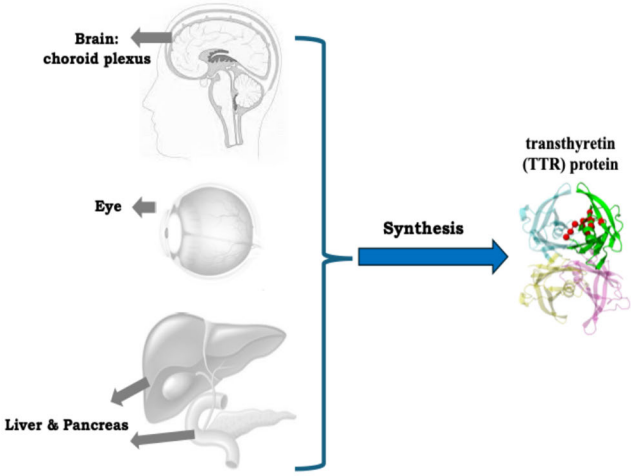

Figure 2: Organ's synthesis transthyretin (TTR) protein. Liver obtains around 90% of TTR in blood stream. TTR expressed by brain circulate in cerebrospinal fluid (CSF) (Created by author)

Structure of TTR

Plasma and CSF fluid contain the 55 kDa homo-tetrameric TTR protein (or pre-albumin.). It is made up of four distinct subunits, each of which comprises 127 amino acid residues and 13,745 Da [1]. Inherent TTR has a spherical form with a dimension of 70 Å×55 Å×50 Å and a core hydrophobic canal. Every monomer contains 8 opposite β-strands (A over H), that are systematized into stranded β-sheets (DAGH and CBEF) and only a small α-helix situated on β-strand E [9]. Each subunit's β-strands F and H engage through hydrogen bonds to create a dimer. The remains of the loops joining β-strands G to H and A to B interact to produce tetramers (Figure 1). The breakdown of TTR tetramers into monomers is facilitated by low pH. The TTR tetramer became unstable due to the double protonation of His88 in the neutral crystal structure, which broke the hydrogen-bond network [10,11].

Physiological Sources and Concentrations of TTR

TTR is mostly produced by hepatocytes [1] and the brain's choroid plexus epithelial cells [12], that are the resources of TTR found in blood and cerebrospinal fluid, accordingly (Figure 2). 90% of human blood TTR is produced by the hepatocytes with range between 20 and 40 mg/dl [1]. TTR circulation content vary with age; in normal neonates, they are lower than in adulthood [13] and begin to drop beyond the age of 50 [14]. According to Vasassery *et al.*, the TTR level in CSF varies between 5 and 20 mg/l or around 25% of the overall protein composition of CSF [15]. TTR is also manufactured in the eye retina [16], in the pancreatic α cells [17] and to a lesser degree in the muscles of the skeleton, gut, myocytes and spleen [2].

Metabolism of TTR

In human beings, TTR has a physiological half-life of two to three days [1]. It was discovered that the keratinocytes, myocytes and hepatocytes were the main locations where TTR was broken down. The hepatocytes accounted for 36-38% of the body's total TTR breakdown, monitored by 12-15 percentage myocytes and keratinocytes (8-10%). The percentage of TTR breakdown in the renocytes, fat cells, testis and the gut ranged from 1 to 8%, while incorporation

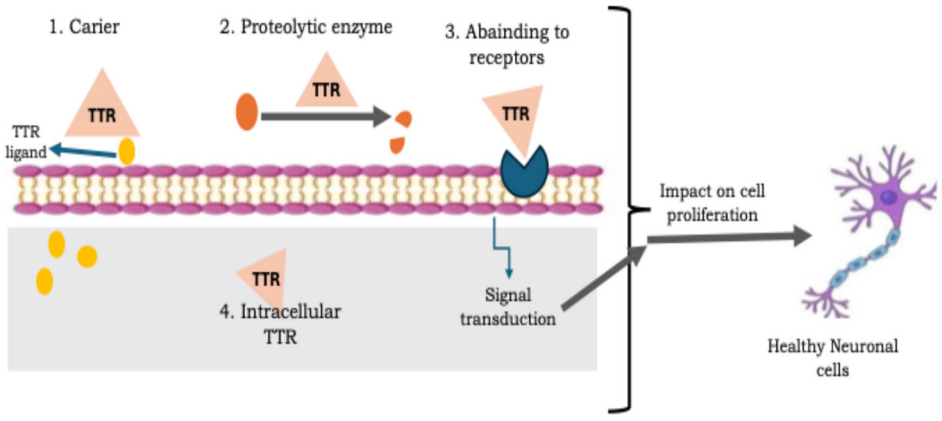

Figure 3: TTR promote neurooritection and immune modulation. 1. TTR carrying hormones, 2. As proteolytic enzyme, 3. Express signal transduction after binding to receptor. Finally, affect intracellular root (Created by author)

in the hepatocytes and renal cells is induced by receptor (Figure 3). It was demonstrated that the megalin receptor, also referred to as low-density lipoprotein-related protein 2 (LRP2), facilitated the renal absorption of TTR [1]. Renal proximal tube epithelium, among different epithelia, generates megalin, receptor related to the low-density lipoprotein (LDL) receptor group. A study illustrated that TTR transportation in hepatocytes was facilitated by LDL receptor group responsive to receptor-associated protein (RAP) [18].

IMPORTANCE OF TTR IN CELL BIOLOGY

Physiological Functions of TTR

TTR is mostly known for its function as a retinol (vitamin A) and T4 carrier protein in BLOOD and brain CSF. Additionally, TTR function role in proteolysis and neuroprotection.

TTR as a Carrier of T4

Thyroid hormones are molecules crucial in growth, cells transformation and metabolic balance management in mammals. The functions these molecules in cell immigration, communications, myelination and stimulation of neuritis development have also been suggested [19]. Tetraiodothyroxine (T4), triiodothyronine (T3) and a biologically inert T3 are the three THs that are produced by the thyroid gland. T4, a highly prevalent TH, binds to thyroxin-binding globulin and released into the blood [1]. The transportation of T4 is one of TTR's biological jobs. Despite having a significant amount in human blood, TTR has a moderate attraction for T4 and only transfers 15% of T4 and 10% by blood albumin; and the remaining released into blood (0.03-0.05%) in a free state [1]. A core hydrophobic channel with two T4 binding sites is formed by the tetrameric configuration of native TTR [11]. TTR only carries one thyroxine molecule because these binding regions have negative interaction [1]. There is no agreement about the transport of T4 in tissue cells; some argue that T4 is taken up while linked to the transport proteins, while others assert that T4 penetrates the cell passively via diffusion after dissociating from the transport molecule. [20]. It was shown that TTR plays a crucial function in T4 transportation through the placenta's walls and transmit to the embryo [21]. Besides, TTR transfers eighty percent of T4 in CSF of human [2].

TTR as a Carrier of Retinol

Vitamin A, also known as retinol and its byproducts are derived from food. This vitamin undergoes oxidation to produce retinoic acid that is crucial for a number of processes, including developmental processes, control of sleep and eyesight [22]. Additionally, it regulates synaptic flexibility, growth of neurons and neuronal longevity in the brain hippocampal regions, olfactory system and hypothalamus [23]. Retinoids can control cell division, neurite development and defence versus free radicals [24]. Several showed that vitamin A has a therapeutic role in neuronal via inhibiting the amyloid fibril formation [25]. Retinol is expressed in liver and released to blood for binding to retinol binding protein (RBP) [26]. Retinol can be delivered to cells via the TTR-RBP complex, which is a highly steady type of retinol transport that is crucial for preventing RBP disintegration [26]. The TTR tetramer contains four RBP-binding sites, two in each dimer at the protein surface. However, each TTR molecule only transports two RBP due to steric hindrance. Under physiological settings, the TTR tetramer only transports one RBP molecule because RBP levels are low in comparison to TTR [27].

Proteolytic Functions of TTR Beyond Transport

TTR's proteolytic activity on a variety of substrates is an additional essential role besides its function in the delivery of T4 and retinol. High-density lipoproteins (HDL) transmit a tiny portion of circulating TTR (1-2%) via joining to apolipoprotein (apo) A-I [28]. The TTR-apoAI binding was studied, TTR was identified as an unconventional serine protease that can cleave the carboxyl terminal region of apoA-I [29] and to decrease outflow of cholesterol [30]. Additionally, TTR can break down the Aβ peptide and neuropeptide Y (NPY) [31]. Aβ can be broken at various points and when matched to the entire peptide, the resultant peptides have been demonstrated to have a lower amyloidogenic potential. Furthermore, TTR can break down accumulated variants of Aβ; when TTR activity declined, the development of Aβ fibrils accelerated [31].

Neuroprotection of TTR

According to research, TTR may play a biological role in memory and learning as well as in the renewal of the central nervous system (CNS) and peripheral nerve system (PNS) [32,33]. One of the main Aβ-binding molecules is TTR molecule [31]. According to Costa *et al.* [32], TTR can break down the soluble and accumulated variants of Aβ, reducing its harmful effects and formation of fibrils while enhancing neuroprotection by modifying brain Aβ levels in people with Alzheimer's [34]. Amyloid-β (Aβ) deposits build up in the nervous system during Alzheimer's illness, which causes a gradual impairment of brain function. By interacting with Aβ and blocking its buildup, TTR assists in avoiding dementia [35]. Furthermore, TTR affects Aβ elimination through the brain's export of Aβ and the liver's internalisation of it through Lipoprotein-related receptor 1 (LRP-1) [36]. TTR prevents the brain from focal cerebral ischaemia [37]. For people with stroke, a lower blood TTR is thought to be a reliable indicator [38]. Through its binding with megalin receptor, TTR stimulates the neurite regeneration, leading to an increase of calcium in the cell and a Src/ErK/Akt/CREB pathway [39]. Likewise, TTR/megalin interaction stimulates antiapoptotic genetic material, including those in the Bcl2 molecule family, which reduces neuronal apoptosis by triggering the cAMP response element-binding protein (CREB) [39]. By interacting to and enhancing the production of IGF1-R in hippocampus neurons, TTR has also been demonstrated to trigger the

induction of the insulin-like growth factor 1 receptor (IGF1-R)-protein kinase B (PKB or AKT) signalling cascade [40]. It has been discovered that TTR's stimulation of the IGF1-R signalling mechanism regulates synaptic action, neurite development and neuroplasticity and this may, partly, explain the neurogenic and neuroprotective effects of TTR [41]. Brain can be protected from GABAA-R-mediated neurotransmission, which is implicated in epilepsy, anxiety, depression, schizophrenia and autism, by TTR's ability to control GABA (γ-aminobutyric acid) A receptor (GABAA-R), which is crucial in suppressing neuronal activity [41].

TTR Regulates Cell Metabolism in CNS

It has been demonstrated that TTR increases the production of ATP via inducing the generation of glycolysis controllers in astrocytes, specifically phosphofructokinase P (PFKP) and pyruvate kinase M1/M2 variants (PKM1/2) [42]. Zawiślak *et al.* [41] also linked TTR to the metabolism of astrocytic energy, which in turn affected brain energy, glia-neuron connections and neuroplasticity. Two downstream processes, the MAPK/ERK and PI3K/AKT/mTor processes, are triggered by IGF1-R and influence a number of cellular activities, including differentiation, proliferation and protection from apoptosis [43]. Vieira *et al.* [44] revealed TTR as an inducer of the IGF1-R pathway in the CNS, suggesting that TTR, possibly via IGF1-R, may have pivotal roles in metabolic regulation in different cell types and in maintaining cellular health and function. Moreover, a study demonstrating that TTR induces glycolysis in astrocytes and controls energy generation in astrocyte [42], as well as break down of glycogen which is important for neuroplasticity and formation of memory [45], provide more evidence in favour of TTR's classification as a crucial molecule for memory formation and neuroplasticity.

Immune Regulation of TTR

It has been demonstrated that TTR regulates myeloid cell development to regulate immune cell reaction [46]. All immune system cells, including granulocytes, macrophages, dendritic cells and mast cells, are descended from myeloid lineage cells [47]. As a result, TTR has been shown to promote cell development in the bone marrow's myeloid compartment [46], which may indicate that TTR regulates the immune system (Figure 4).

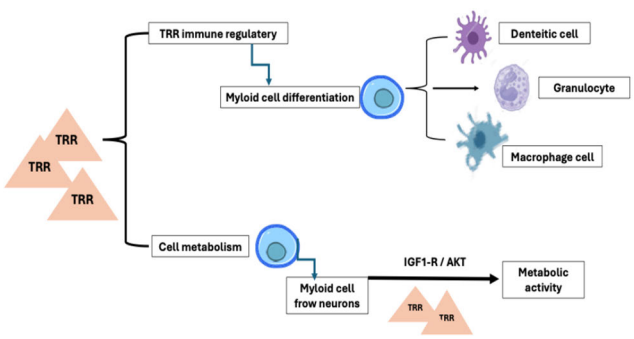

Figure 4. TTR role in immunity and β cell metabolism (Created by author)

ROLE OF TTR IN AMYLOIDOGENESIS

Protein fibrils that accumulate throughout tissues are a hallmark of amyloidosis that can lead to many diseases due to organ dysfunction. These fibrils are derived from one of at least 18 known precursor proteins, with each precursor protein being associated with a specific form of amyloidosis. Whatever the kind of precursor, total amyloid fibrils have a width of about 10 nm [48].

TTR is the cause of a unique class of illnesses because of conformational alteration in the TTR molecule leading its misfolding and miss its tetrameric structure. This may result in the development of unsolvable amyloid fibrils that accumulate in tissue extracellularly and have the β-pleated sheet shape. The unsolvable amyloid fibrils accumulate with each other and with the components of extracellular matrix to generate bulky amyloid plaques [48]. These fibrils have a typical twisted β-pleated-sheet structure, are solid, non-radiating and vary in size, ranging from 7 to 10 nm. The fibril formation process of TTR. When these amyloid plaques build up excessively, it causes dysfunction of the impacted organs [48].

Types of TTR Amyloidosis (ATTR)

There are two main types of ATTR amyloidosis: familial or hereditary ATTR (ATTRv) amyloidosis and wild-type ATTR (ATTRwt) amyloidosis [49].

Wild-type ATTR Amyloidosis

Men over 60 are typically affected by this type, which develops with age and mostly affects the heart for an undisclosed reason [50].

Hereditary ATTRv

A mutation in the TTR gene that is hereditary, meaning it runs in families. The mutation produces an aberrant TTR protein that is prone to instability and misfolding, resulting in clumps that accumulate as amyloid plaques in different organs. Multiple system problems, including as those affecting the kidney, gastrointestinal tract and nervous system, can be brought on by ATTRv (Figure 5) [51-53].

Pathogenesis of ATTRv and ATTRwt

TTR's biological function includes transferring retinol-binding protein- vitamin A complex and T4 and it may potentially have

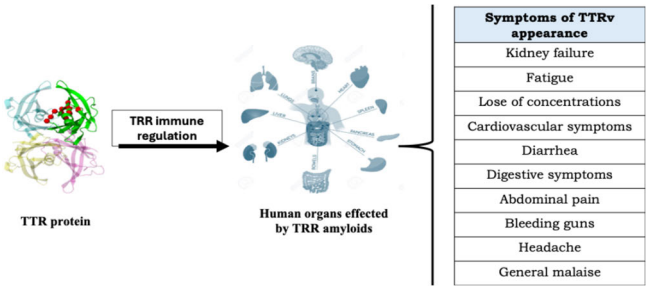

Figure 5: Symptoms indicating to TRRv existences (Created by author)

neuroprotective qualities. Although the pathophysiology of organ injury in ATTR is currently unclear, it has been suggested that tissue specificity of amyloid formation may be determined by local characteristics of endoplasmic reticulum-helps TTR folding and breakdown [54]. The peripheral nerve and the heart muscle are the two main sites where ATTR accumulates in ATTRv. It is thought that the earliest blood-nerve barrier disturbance in the peripheral nerve makes it easier for blood TTR to enter and for amyloid to accumulate [55]. Neurons subjected to amyloid plaques and non-fibrillar TTR may become toxic and mechanical tension may play a part in amyloid fibril extension [56]. The same changes were noted in the choroid and retinal blood vessels, indicating a possible disturbance of the blood-retinal barrier that could encourage the buildup of amyloid in the eyes [57]. In the cardiac muscles, ATTR plaques cause stiffness and decreased contractility of myocytes [58]. TTR tetramer fragmentation is the primary process of amyloid production in ATTRv and the majority of TTR pathogenic genetic alteration cause an unstable TTR tetramer, which facilitates its disintegration into monomers [59]. Folding error in monomers is accompanied by oligomer clump and creation of extended TTR amyloid fibrils [59]. Physiological mild fragmentation and accumulation can ultimately result in ATTRwt [60]. Furthermore, enzymatic breakdown in the other TTR amyloid process results in the generation of carboxyterminal TTR segments, which are more likely to join together to create small amyloid fibrils. Late onset ATTRv and ATTRwt may be related to enzymatic mechanisms [61].

Clinical Disorders of ATTRv

Neurological Features of ATTRv Amyloidosis

ATTRv Amyloidosis Neuropathy: ATTRv amyloidosis has found to cause little fibre neural damage and big fibre poly-neural damage in persons have similar genetic changes. Autonomic short fibre nerve damage is the early-onset traits (injury to the neurons disrupts signals conveyed between the brain and different bodily system [62]. The existence of all responsiveness and motor deficits (including weakness, exhaustion, altered feeling, decreased balancing, muscle contraction and impaired coordination) become obvious with length-dependent progression once the disease progresses and larger fibres are destroyed [62]. However, with the Val30Met late-onset illness, loss of feeling with muscle damage are common symptoms, resulting walk dysfunction. This is because larger myelinated fibre injury is prevalent over microscopic nerve fibre damage [62]. Neuropathic inflammation and alteration of feeling for pain are the hallmarks of small-fibre neuropathic; proprioception and tactile sensitivity are unaffected [63]. Physicians use neurological signs to inform their diagnosis, which is then verified by skin biopsy [64]. Large fibre neuropathy linked to ATTRv is usually marked by a sensory axonal nerve damage that progresses quickly and becomes incapacitating [53]. Patients with extreme neuropathic may eventually become immobile or dependent on a wheelchair [65].

ATTRv Amyloidosis Autonomic Dysfunction

Autonomic dysfunction is often regarded as the initial symptoms in the early phases of illness and is associated with early amyloid plaque accumulation in the sympathetic and dorsal root ganglia [55]. Erectile impairment, dryness in the eyes and mouth, decreased sweating, anomalies of the bladder and changes in bowel movement are all signs of autonomic dysfunction [66]. Patients with ATTRv may exhibit a range of gastrointestinal indications, including frequent vomit and nausea, inability to eat and stomach distension of the abdomen, diarrhoea, and/or constipation [55]. Managements of signs are essential to recover the feature of life of subjects

ATTRv Amyloidosis Stenosis of Lumbar Canal

Decreasing in spinal channel diameter, known as lumbar canal stenosis, causes pressure on the nerves and spinal cord [67]. With an incidence of 1.7-13.1% in the majority of the people, it usually impacts those over 50 [67]. Lesser limb pain, along with cramping leg muscles, are the most prevalent signs that patients describe [67]. The flavum ligament thickening that causes lumbar canal stenosis could be an early clinical sign of ATTRv [68]. Finding the accumulation of amyloid in individuals following orthopaedic operations is not unexpected because it may happen in any tissue, including synovial tissue [69]. Amyloid plaques were found in all 95 flavum ligament specimens removed from individuals suffering from spinal cord stenosis. the investigation showed that 45% of these specimens revealed TTR positive [70]. Consequently, although lumbar canal stenosis does not distinguish between hereditary and non-hereditary driven types, it may be regarded as a sign of a potential amyloid buildup.

Ocular Amyloidosis

Ten percent of people with ATTRv have visual impairment, which typically manifests later in the disease's progression. These conditions include corneal nerve damage, aberrant conjunctival vessels, vitreous opaque regions, keratoconjunctivitis sicca and chronic open-angle glaucoma (COAG) [71]. A common ocular feature known as a "scalloped pupil", characterized by uneven pupillary margins and fringed edges may be cofound in ATTRv cases [72].

Brain /CNS Amyloidosis

Brain amyloidosis is due to the continual generation of amyloid plaques by the retinal and plica choroidea [73]. TTR amyloid can buildup in the cerebral microvasculature, under the arachnoid membrane. and brain surface [74]. The brain surface amyloidosis, a condition named as hereditary oculoleptomeningeal amyloidosis [75]. Medical signs include brain micro-vessels ailment and ischemia, cerebral bleeding, cognitive deficiency and seizure [73]. Temporary recurrent attacks of neurological manifestations, often known as "amyloid spells," are the commonly recorded symptoms. These cases are typified by recurrent, stereotypical clinical episodes that typically involve

unfavourable symptoms, including loss of sensation or focal muscular weakness [73]. Whereas CSF investigation is not particularly indicative and typically reveals high levels of CSF proteins, MRI investigations can identify brain surface intensification and finally may be useful in guiding brain biopsy [76]. When old people suffer of cognitive problems or repeated vascular episodes, it's critical to consider the potential cerebral contribution of ATTRv [76].

ATTRv Non-Neurological Amyloidosis

Transthyretin Amyloid Cardiomyopathy (ATTR-CM): One form of systematic amyloidosis where misfolded of TTR molecule accumulates in the heart is called transthyretin amyloid cardiomyopathy (ATTR-CM). TTR protein is carried by the genetic material 18. So, an alteration in the genetic factor expressing TTR can result in configurationally alteration in TTR, leading to mis-folding. This kind of ATTR is named as heritable TTR amyloid (hATTR). Besides, in elderly ATTR tetramer can undergoes misfolding [77]. This kind of ATTR is called ATTRwt [50]. Transthyretin amyloid cardiomyopathy (ATTR-CM) is a medical disorder caused by accumulation of misfolded TTR in heat muscles in both ATTR types (hATTR and wATTR). Nevertheless, new medical research indicates that wATTR-CM is more prevalent than hATTR [78].

Pathophysiology of ATTR-CM

TTR protein misfolding, can produce amyloid fibrils that buildup in the myocytes triggering amyloidosis-cardiomyopathy resulting in myocardial stiffening, fibrosis and heart conduction block or arrhythmia which ends with myocardial dysfunction [79]. TTR deposition also causes myocardium thickening, hypertrophy and diastolic impairment. In progressive phases, abnormality in cardiac function can cause reduced systolic function [80].

Renal Amyloidosis

Nephrotic disorder and irreversible kidney damage are brought on by infiltrative renal amyloidosis [81]. Renal amyloidosis, which has only been recorded in valine at amino acid 30 to methionine ATTRv individuals and is uncommon in nonhereditary persons, is present in about 1/3 of the individuals in endemic regions and 6% of individuals in nonendemic regions [81]. Different distributions of amyloid renal plaques were found, including basement membrane of renal tubes, pericapsular, blood vessels and the medulla and interstitium of cortex [81].

Gastrointestinal Amyloidosis

According to the kind of genetic changes, the incidence of digestive tract amyloidosis seems to range from 56 to 69% [82]. There are many different intestinal symptoms, but the most prevalent ones are steatorrhea, diarrhoea and uncontrollable loss of weight. These symptoms frequently present before constipation or neuropathy-related problems. More rarely, a particularly dire prognosis has been shown for potential intestinal blockade, which typically does not cure with pro-motility medications. Hepatomegaly indicated by high serum liver enzyme indices is also common [81].

Amyloid Myopathy

Myopathy, an uncommon symptom of ATTRv, is thought to be caused by muscle injury associated with amyloid buildup in muscles, particularly in the perimysium [82]. On electromyography studies, impacted individuals exhibit myogenic alterations and proximal weakness. Amyloid muscle damage may go undiagnosed because it might be difficult to differentiate between muscle and nerve dysfunction clinically [82].

Feedback Mechanisms that Inhibit the Amyloid Cascade

Transthyretin (TTR) exhibits (feedback inhibition mechanisms) primarily through ligand-induced stabilization of its native tetrameric structure, preventing dissociation into amyloidogenic monomers.

TTR Stabilizers

Thyroxine (T4) Binding: T4 stabilizes the TTR tetramer by attaching to its thyroxine-binding pockets, reducing dissociation into monomers. This suppresses accumulation of amyloid fibril [83]. Mechanism: T4 binding increases thermodynamic stability, slowing tetramer dissociation (half-life extended from hours to days) and reducing aggregation risk.

TTR Kinetic Stabilizers

TTR kinetic stabilizers are substances that attach to TTR specifically and stop it from dissociating. Since the ensuing processes of protein misfolding and amyloid fibril production depend on the dissociation of TTR tetramers into monomers [84]. It has been suggested to use little molecules that attach to thyroxin binding sites to stabilize the native structure of TTR tetramers as a potential approach for the treatment of both ATTRv and ATTRwt [85]. As these TTR-stabilizing drugs such as tafamidis can be administered orally for ameliorating the progress of neural damage in ATTRv subjects as well as cardiomyopathy resulting from both ATTRv and ATTRwt amyloidosis [86,87].

Tafamidis

A homologue of thyroxine called tafamidis is intended to stabilize the quaternary form of TTR [88]. The FDA accepted tafamidis to treat myopathy resulted from ATTR. The drug attaches itself specifically to the TTR thyroxine-binding sites. By stabilising the tetrameric state and delaying breakdown into monomers, it lowers the production of amyloid. It may not be able to correct the condition, but it can delay its worsening by preventing more ATTR buildup. To see the clinical benefits in treating myopathy, treatment with tafamidis must be begin quickly [87].

MOLECULAR THERAPY

Antisense oligonucleotides (ASO) or small interfering RNA (siRNA) are the mainstays of gene silencing techniques

created to treat ATTRv [89]. Recently, Inotersen (ASO) and Patisiran (siRNA) were licensed to cure reasonable phases of ATTRv [89].

ASO

According to Benson *et al.* [49], inotersen is an ASO that ultimately limits tissue accumulation by lowering blood TTR concentrations. It is given subcutaneously once a week and preferentially binds TTR mRNA, triggering its breakdown and preventing the creation of both mutant and wild type forms [49].

siRNA

A genetically constant nucleotide in the 3′ un-translated area of entire variations and TTR mRNA is the particular target of the siRNA patisiran. Formulated as nanoparticles of lipid, patisiran is infused intravenously and travels to the liver, which is the main location where TTR molecule is found in the bloodstream. Liver' apolipoprotein E receptors detect the apo-lipoprotein formulated as nanoparticle's lipid pill and endocytosis internalises the medication to deliver the siRNA to the liver. Blood TTR molecule can be eliminated Via breakdown by Patisiran (RNAi) [90].

Organ Transplantation

Mutant TTR can be eliminated from the bloodstream by hepatic transplantation. Although it has been used to treat hATTR in the past, wATTR cannot be treated with it [91]. The necessity for liver transplants has significantly decreased since the development of TTR-specific treatments. Although some subjects with amyloid myopathy may potentially receive combined hepatic and cardiac transplants, this is rarely the case in clinical practice because these individuals are frequently elderly and have low long-term survival rates [92].

CONCLUSIONS

Transthyretin (TTR) is a multifunctional protein primarily synthesized by hepatocytes and the choroid plexus epithelium, where it contributes to the transport of thyroxine and retinol through its interaction with retinol-binding protein. Beyond its classical transport role, emerging evidence indicates that TTR participates in maintaining cellular homeostasis, exhibits neuroprotective and proteolytic properties and may influence immune regulation and inflammatory responses. Structural destabilization of TTR can lead to protein misfolding and amyloid fibril deposition in various organs, resulting in transthyretin amyloidosis (ATTR).

ATTR includes both hereditary (ATTRv) and wild-type (ATTRwt) forms, which primarily manifest as cardiomyopathy and polyneuropathy. Current therapeutic strategies, including TTR stabilizers (e.g., tafamidis, diflunisal), gene-silencing agents (e.g., patisiran, inotersen) and liver transplantation, can slow disease progression** but do not provide a complete cure.

Future Recommendation

Future research should focus on elucidating the immunological and cellular mechanisms underlying TTR misfolding and aggregation, as well as their contribution to organ-specific pathology. A deeper understanding of these pathways could pave the way for novel immunomodulatory or gene-based therapies that target both the molecular and immune aspects of TTR-related disorders.

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