Transthyretin: Osteoarticular and Cardiovascular Diseases

Subjects: Cell Biology

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Definition

Transthyretin (TTR) is a tetrameric protein transporting hormones in the plasma and brain, which has many other activities that have not been fully acknowledged. TTR is a positive indicator of nutrition status and is negatively correlated with inflammation. TTR is a neuroprotective and oxidative-stress-suppressing factor.

1. TTR Structure and Major Functions

Human TTR (UniProtKB, P02766) is a homotetrameric, slightly acidic (isoelectric point of 5.3) protein with a molecular weight of 55 kDa (Protparam, https://web.expasy.org/protparam/) that binds and transports thyroid hormones and retinol in the plasma and cerebrospinal fluid (CSF) [1][2]. TTR is synthesized predominantly in the liver and choroid plexus [3][4]. However, TTR is also present in kidneys, the pineal gland, and in certain types of cells, such as neurons, retinal pigment epithelium, or pancreatic island cells [2][5][6][7][8][9]. TTR expression in the liver is controlled by hepatocyte nuclear factors [10]. In the brain, TTR synthesis is enhanced by heat shock factor 1 [11] and mitochondrial transcription factor A (TFAM) [12]. Stress and steroid hormones, phenylalanine, and its metabolites also regulate TTR expression [9][13][14]. The central ligand-binding channel is formed when four TTR monomers assemble into the complex [15]. This hydrophobic cavity is able to accommodate up to two thyroxine molecules. However, due to negative cooperativity, TTR carries only a single thyroxine molecule [16]. In plasma, human TTR binds, with intermediate affinity, 15–20% of the thyroid hormone pool, complementing the transport provided by thyroxine-binding globulin and albumin. However, TTR is the major thyroid hormone-binding protein in CSF [17][18]. This binding protects thyroid hormones from adsorption on lipid phases; therefore, almost all hormone molecules circulate in a protein-bound form [18]. On the other hand, only a small population of TTR molecules carry the ligand because TTR concentration greatly exceeds the thyroid hormone level in both plasma and CSF [17][19][20][21]. The central channel of TTR can also tolerate multiple other natural ligands, including lutein and other carotenoids, curcumin, polyphenols (resveratrol), norepinephrine oxidation products, and other compounds [1][22][23][24]. TTR also distributes retinol complexed with retinol-binding protein (RBP), and the binding stoichiometry is 1:1:1 [25]. RBP binding is able to influence physiological function of TTR. RBP abrogates the binding of soluble TTR to receptor for advanced glycation end products (RAGE) [26]. Aggregated (fibrillar) TTR activates nuclear factor κB through interaction with RAGE and induces inflammatory and apoptotic responses [26]. Additionally, the interaction of TTR with perlecan, a component of the basement membrane, is negatively influenced by RBP [27]. Approximately 1–2% of TTR molecules circulate in the plasma in association with high density lipoproteins (HDL) due to the binding to apolipoprotein A1 (ApoA1) [28]. However, the interaction of TTR with ApoA1 is not affected by RBP [28]. The neurogenic effects of TTR are also not dependent on its ligands: RBP and thyroxine [29]. TTR has neuroprotective functions and/or is a stress response factor in various adverse conditions, including ischemia, Alzheimer's disease (AD), Crohn's disease, osteoarthritis, and preeclampsia [29][30][31][32][33]. Interestingly, RBP, by stabilizing TTR structure, reduces the inhibitory effect of TTR on Aβ aggregation [34]. In addition to neuroprotection and neurogenic activity, TTR is engaged in insulin secretion, autophagy, memory, and behavior [35][36][37][38][39]. TTR is a diagnostic marker positively correlated with nutrition, for both protein and glucose metabolism, and negatively correlated with acute inflammatory states [40]. Importantly, TTR is a Zn 2+ -dependent protease (also active in the presence of Mn 2+ , Fe 3+ , and Co 2+) that cleaves ApoA1, neuropeptide Y (NPY), and amyloid β (Aβ) peptide [41][42][43].

2. Involvement of TTR in Biomineralization

Proteomic analysis identified TTR as one of the proteins specifically associated with mammillary cones and important for the initial phase of eggshell biomineralization in chicken [44]. Investigation of the ability of TTR to influence the formation and morphology of calcium carbonate crystals demonstrated that extensive and amorphous deposits of human TTR are associated with crystals with unique morphology [45]. Additionally, various amyloid-like TTR forms, which remodel crystal faces, were present on the inner and outer surfaces of the crystals [45]. Morphology of large crystals is strikingly similar to that of the crystals obtained in the presence of MRCP20 protein, which is involved in biomineralization of the cement of barnacle Megabalanus rosa [45][46][47]. MRCP20 initiates the formation of amyloid-like fibrils on the surface of mineral crystals through stable β-sheet motives [48]. Some calcium carbonate crystals grown in the presence of TTR were small and rod-shaped [45]. Rod-shaped structures were also observed in the barnacle cement [49], indicating functional similarity between MRCP20 and TTR. Currently available information about the nucleation stage of biomineralization indicates the importance of the amyloid and disordered protein components in the formation of the polymer-induced liquid phase (PILP) in the presence of ions [50][51]. Thus, it was postulated that TTR amyloid may play a functional role in biomineralization, e.g., in the cement line, which constitutes the mineralization front between the subchondral bone and calcified cartilage [45][52].

3. TTR Interconnection with Inflammation

The deposition of aggregated proteins (including fibrin) activates tPA and factor XII [53]. tPA activation directly leads to an increase in plasmin levels (an increase in fibrinolytic activity). On the other hand, the activation of factor XII leads to the activation of the intrinsic coagulation pathway and results in the formation of bradykinin, a vasoactive peptide that promotes/induces multiple inflammatory responses [53].

On the other hand, properly folded TTR is a negative marker of inflammation and a positive marker of nutrition status, guarding the homeostasis of protein synthesis and breakdown [32][40]. However, elevated ROS, oxidative modifications, and aging negatively affect the structural stability of proteins in general, and TTR in particular, and lead to TTR aggregation [54][55][56][57]. In turn, TTR amyloid induces a cytotoxic response that involves ER stress, dysregulation of Ca 2+ balance, induction of UPR, upregulation of MMPs, apoptosis, and binding of membrane lipids [58][59][60][61][62]. Consequently, TTR amyloid contributes to oxidative stress and progression of inflammation [63][64][65][66]. In the plasma of FAP patients, the levels of cytokines (such as TNF-α, IL-1β, IL-8, IL-33, IFN-β, IL-10, and IL-12) are altered compared to those in healthy individuals [66]. Changes in cytokine levels were also observed in asymptomatic FAP patients, indicating that the induction of inflammation precedes amyloid fibril deposition [66].

Stabilization of proper TTR structure reduces cytotoxicity induced by TTR aggregates and improves survival of patients with ATTR CA [67][68]. However, the factors that reduce oxidative stress, such as tauroursodeoxycholic acid (TUDCA), were also shown to lead to a reduction in toxic aggregates of TTR [65]. TUDCA does not affect the stability of TTR in vitro, suggesting that the association of TTR with oxidative stress and inflammation is indirect and bidirectional, and that oxidative stress leads to TTR destabilization and amyloid formation [65]. This bidirectional relationship between amyloid and inflammation also occurs in AD. Aβ peptide deposits induce immune response, and molecules involved in inflammatory processes can increase the formation of Aβ [69][70]. Interestingly, inflammatory processes that lead to Aβ deposition are induced by peripheral plasmin [69]. Chronic inflammation leads to amyloidosis, and amyloid activates immune signaling [71][69][70]. Since inflammation, in turn, accelerates protein aggregation, this interconnection drives vicious cycle 3 (**Figure 1** B).

In blood exposed to inflammatory concentrations of hypochlorous acid, the oxidation of amino acid residues and dityrosine crosslinking of TTR with other plasma proteins (such as α1-antitrypsin, haptoglobin, and albumin) was detected [57]. HMW aggregates of oxidized proteins also include α, β, and γ fibrinogen chains, apolipoprotein A1, and complement C3. In vivo, hypochlorous acid is produced by myeloperoxidase (MPO), which is present in mammalian neutrophils, monocytes, and some subtypes of

tissue macrophages [62][72]. MPO is the key enzyme in the host innate immune defense against pathogen infection [62][72]. Elevated levels of MPO activity in the plasma are observed in myocardial infarction and in ACS, and high MPO concentrations are associated with major adverse cardiovascular events in patients with CAD [62][73][74]. The yin and yang action/dual nature of MPO is manifested by the destruction of invading pathogens and MPO involvement in disease progression and harmful effects on the host tissues [62].

4. TTR Regulation of Angiogenesis

Transcriptome analysis of human retinal endothelial cells (hRECs) in diabetic retinopathy (DR) revealed the regulatory network of protective functions of TTR, implying that TTR co-ordinates oxidative stress, inflammation signaling, autophagy, and apoptosis in DR [75]. DR is a serious microvascular complication of diabetes mellitus caused by hyperglycemia and hypoxia due to metabolic imbalance. Under hypoxic conditions, TTR interacts with and upregulates GRP78 and acts as a trigger of apoptosis of hRECs, which leads to the suppression of neovascularization [21][76]. Under hyperglycemic conditions, TTR represses angiogenesis by inhibiting the proliferation of hRECs through the tyrosine protein kinase receptor 2 (Tie 2) signaling pathway [77]. TTR also suppresses the proliferation of hRECs by long noncoding RNA (lncRNA) MEG3 in the miR-223-3p/FBXW7/Notch1 signaling pathway [78][79]. Therefore, TTR regulates lncRNAs to repress vascular leakage in the retina [75][79]. TTR is also able to regulate and interact with vascular endothelial growth factor [77][80].

Neovascularisation plays an important role in wound healing and atherosclerosis [81][82]. HDL transports miR-223 and other miRNAs [83][84], and signaling of multiple noncoding RNAs is involved in the progression of atherosclerosis [85]. Some lncRNAs are involved in VSMCs phenotype switching. For example, MALAT1/miR-204/SMAD4 regulates osteoblastic differentiation of human aortic valve interstitial cells in CAVD, and TUG1/miR-204-5p promotes osteoblastic differentiation by upregulating Runx2 in aortic valve calcification [85]. lncMEG3 is one of the lncRNAs responsible for pathological cardiac remodeling in atherosclerosis and ECM reconstruction [86], and MEG3 was shown to be downregulated in CAD [87]. The MEG3/miR-223/NLRP3 inflammasome pathway has been shown to enhance inflammatory cell death (pyroptosis) in human aortic endothelial cells [88]. It is of interest to determine whether TTR (directly or indirectly through HDL) regulates the MEG3/miR-223-3p/FBXW7/Notch1 signaling pathway in atherosclerosis.

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Keywords

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