HuR and other turnover- and translation-regulatory RNA-binding proteins: implications for the kidney

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POSTTRANSCRIPTIONAL REGULATION plays an indispensable role in human biology and has recently been recognized to play important roles in renal physiology and pathobiology. As part of an adaptive response, the posttranscriptional regulation complements the transcriptional one, influencing the expression of >50% of stress-regulated genes (23). The stages of posttranscriptional regulation include pre-mRNA splicing, maturation, transport, editing, localization and storage, turnover, and translation (66). Among these, the control of mRNA stability and translation are not only best characterized but also very rapid and effective processes of the adaptive response. This level of regulation is particularly important to ensure the production of proteins in the appropriate time, amount, and location, all of which have profound physiological effects.

Posttranscriptional regulation requires trans factors represented by noncoding RNA [especially micro(mi)RNAs] and turnover- and translation-regulatory (TTR) RNA-binding proteins (RBPs). These multifactorial proteins are a group of heterogeneous RBPs primarily implicated in controlling the decay and translation rates of target mRNAs. TTR-RBPs usually shuttle between cellular compartments (the nucleus and cytoplasm) in response to various stimuli and undergo posttranslational modifications such as phosphorylation or methylation to ensure their proper subcellular localization and function. TTR-RBPs are emerging as key regulators of a wide variety of genes influencing kidney physiology and pathology. This review summarizes the current knowledge of TTR-RBPs that influence renal metabolism. We will discuss the role of TTR-RBPs as regulators of kidney ischemia, fibrosis and matrix remodeling, angiogenesis, membrane transport, immunity, vascular tone, hypertension, and acid-base balance as well as anemia, bone mineral disease, and vascular calcification.

RNA-binding protein; RNA turnover; renal; nephrology
RBPs were identified (7). This indicates great combinatorial variability and profound role of posttranscriptional gene expression network (7, 48).

**TTR-RBPs and Their Renal Aspects of Function**

The basic cellular functions of major TTR-RBPs known to play a role in renal physiology are shown in Table 1 (11). In this section, we will discuss the actions of TTR-RBPs in posttranscriptional regulation in renal homeostasis and in the adaptive responses contributing to the pathogenesis of various renal diseases. We will focus on separate processes, such as ischemia, fibrosis and matrix remodeling, angiogenesis, transporter expression, immunity, vascular tone, hypertension, and acid-base balance, rather than a description of separate disease entities.

**Ischemia.** Using energy depletion as an ischemic injury-mimicking model, HuR was shown to swiftly translocate into the cytoplasm upon ATP depletion in the LLC-PK1 epithelial cell line, a process that was more rapid after a repeated round of ATP depletion (43). The translocation was followed by increased total HuR protein levels without changes of RNA expression. In a rat model of ischemia-reperfusion injury, intracytoplasmic levels of HuR also increased postischemia, primarily within cells of the proximal tubule (6). HuR knockdown led to increased apoptosis in cultured renal tubular cell lines (LLC-PK1 and HK-2) upon ATP depletion, whereas HuR overexpression was protective against apoptosis induced by the same stress (6).

As a possible mechanism, it was proposed that HuR upregulation during ATP depletion increases the expression of the adapter protein growth factor receptor-bound protein 10, which promotes the activation of Akt, a member of the serine/threonine kinase family phosphorylating several cell survival and apoptosis-regulating proteins, including Bcl-2, caspases, and their inhibitors (80). Activated Akt, in turns, also stimulates NF-κB, which increases HuR expression by transcriptional control, thus closing the positive regulatory loop (80). In addition, HuR itself stabilizes numerous antiapoptotic genes (Bcl-2, prothymosin-α, and X-linked inhibitor of apoptosis), including its own mRNA, further amplifying this regulatory pathway (5, 14, 72, 82).

HuR has been shown to promote the stability of STE20-like kinase, which is a renal epithelial kinase whose activity is elevated during embryonic development and recovery from acute kidney injury. This enzyme, on the other hand, has proapoptotic functions, making HuR regulation of cell survival more complex (13). Our laboratory has shown that immune responses are important in the pathogenesis of renal ischemia-reperfusion injury and that certain T cell subsets have a protective role in a mouse ischemia-reperfusion injury model. There was an intracytoplasmic translocation of HuR upon ischemia-reperfusion injury in a splenic T cell population. Unlike in tubular cell lines, there was no change in total protein levels, but there was an increase in HuR mRNA levels (73).

Taken together, these data suggest that the HuR expression pattern might differ between studied cell types, possibly reflecting a different set of regulated transcripts, and different effector as well as intrinsic cellular functions.

**Fibrosis and matrix remodeling.** Fibrosis and matrix remodeling are integral parts of the pathogenesis of chronic inflammatory and ischemic renal impairment.

Mesangial cells secrete regulatory proteins responsible for the turnover of the extracellular matrix, many of which are regulated at the posttranscriptional level. Matrix metalloproteinase (MMP)-13 has high expression in the mesangial matrix, and its expression is important in conditions where rapid remodeling of the extracellular matrix is needed. It has been demonstrated to have species-dependent expression, regulated by an alternatively spliced T cell-restricted intracellular antigen-1-related protein (TIAR) variant, which selectively binds human MMP-13 mRNA and represses its translation (88). In rat mesangial cells, HuR has been shown to promote MMP-9 expression by stabilizing MMP-9 mRNA. This process is negatively regulated by nitric oxide (NO) in a cGMP-dependent matter (4). On the other hand, increased MMP-9 mRNA stability was seen after treatment with ATP, a process likely mediated by the phosphorylation of HuR by PKC (40).

<table>
<thead>
<tr>
<th>RNA-Binding Protein</th>
<th>Size, kDa</th>
<th>Major functions</th>
</tr>
</thead>
<tbody>
<tr>
<td>HuR</td>
<td>Human antigen R</td>
<td>36</td>
</tr>
<tr>
<td>AUF-1</td>
<td>AU-rich element RNA-binding protein-1</td>
<td>Four isoforms: 37, 40, 42, and 45</td>
</tr>
<tr>
<td>TIA-1</td>
<td>T cell-restricted intracellular antigen-1</td>
<td>40</td>
</tr>
<tr>
<td>TIAR</td>
<td>T cell-restricted intracellular antigen-1-related protein</td>
<td>40</td>
</tr>
<tr>
<td>TTP</td>
<td>Tristetraprolin</td>
<td>34</td>
</tr>
<tr>
<td>YB-1</td>
<td>Y box-binding protein</td>
<td>36</td>
</tr>
<tr>
<td>hnRNP K</td>
<td>Heterogeneous nuclear ribonucleoprotein K</td>
<td>51</td>
</tr>
<tr>
<td>DJ-1</td>
<td></td>
<td>20</td>
</tr>
</tbody>
</table>
Cyclooxygenase (COX)-2 is also involved in the matrix remodeling of chronic inflammatory renal disorders and various models of renal injury, and it has been hypothesized to have antiapoptotic and proinflammatory activity in mesangial cells (27). It has been demonstrated that HuR regulation of COX-2 expression at the posttranscriptional level is one of the underlying mechanisms of ANG II-mediated stimulation of COX-2 expression by mesangial cells (20, 22). The same mechanism of PKC activation and HuR phosphorylation as in the case of MMP-9 likely accounts for the stabilization of COX-2 mRNA and increased COX-2 expression in primary human mesangial cells (20, 22). HuR is not the only TTR-RBP that binds the 3'-untranslated region (UTR) of COX-2, as binding of TIA-1, TIAR, and heterogeneous nuclear ribonucleoprotein (hnRNP) U has been shown as well, although the importance of this interaction at the protein expression level was not shown (10).

ANG II also stimulates plasminogen activator inhibitor-1 expression through HuR-dependent stabilization of its mRNA transcript (21). By exerting ANG II downstream effects on COX-2 and plasminogen activator inhibitor-1, HuR helps to regulate the renal microcirculation, mesangial hypertrophy, proliferation, and extracellular matrix deposition. In addition, HuR also binds renin mRNA and stabilizes its transcript in a cAMP-dependent manner, thus further promoting the renin-angiotensin system (2, 62). Other TTR-RBPs binding renin include hnRNP E, hnRNP K, dynamin, nucleolin, Y box-binding protein (YB)-1, HAHDHP1, poly(C)-binding protein-1, and Munc18-1–interacting protein-homologous protein (81).

An example of an interaction between mRNA and TTR-RBPs in matrix remodeling and fibrosis is an effect of transforming growth factor (TGF)-β on collagen type I-α2 expression. TGF-β increases levels of miRNA-216a, which targets and inhibits a multifunctional molecule with RNA-binding abilities, YB-1, which serves as a translational repressor of the transcription factor Tsc-2. Tsc-2 binds the promoter region and regulates the transcription of collagen type I-α2. In a setting of high mesangial TGF-β levels (e.g., diabetes), miRNA-216a levels are upregulated and YB-1 levels are subsequently reduced, causing diminished translational inhibition of Tsc-2, which leads to higher levels of Tsc-2 and more collagen expression. The net effect is that the TGF-β-triggered cascade leads to enhanced collagen accumulation and cellular hypertrophy (47).

On the other hand, increased YB-1 levels have also been implicated in increasing collagen expression and synthesis (39). It has been observed that upon treatment with cyclosporine A, there is an increased binding of YB-1 to collagen mRNA and its stabilization. On the other hand, the same YB-1 molecule is a translational repressor of its own mRNA. Upon cyclosporine A treatment, YB-1 protein is phosphorylated, which leads to the dissociation of phosphorylated YB-1 from its own transcript followed by enhanced YB-1 mRNA translation and increased availability of the YB-1 molecule for promoting collagen mRNA stability. This effect is mediated by the Akt pathway (39).

It is not clear why the two separate observations showed different effects of YB-1 levels on collagen expression. Different posttranslational modifications (different phosphorylation patterns), species-related differences, or a varying relative importance of each regulation at a given time under different stressors (with a different miRNA pool involvement) may account for these differences, although further experiments are required to reconcile these differences.

YB-1 itself serves as a regulator of TGF-β translation. TGF-β mRNA has two binding sites for YB-1, one with high affinity and one with low affinity. TGF-β translation in proximal tubular cells requires YB-1 binding to a high-affinity site in the 5’-UTR of mRNA, whereas in the presence of high YB-1 levels, binding to a low-affinity site inhibits basal translation (26).

Angiogenesis. In a culture of proximal renal tubular cells, ANG II increases VEGF expression, a process that is controlled by hnRNP K-mediated enhancement of translation. This regulation requires the involvement of Src and PKC-δ; these kinases, in several steps, phosphorylate hnRNP K, which then binds VEGF mRNA and increases its translation (25, 75). In an animal model, hyperglycemia contributes to increased VEGF mRNA translation by ANG II signaling via the ANG II type 2 (AT2) receptor. This was again associated with hnRNP K binding of VEGF mRNA, although the translation enhancement was mostly through elongation phase control and regulated via the Akt-mammalian target of rapamycin signaling pathway (16). HuR has also been demonstrated to regulate VEGF mRNA stability and expression in the HEK-293 cell line under hypoxic conditions (30, 55).

Transporter regulation. Few studies to date have investigated how TTR-RBPs can regulate various tubular exchangers and transporters. In one study (42), HuR was found to regulate E1-V-ATPase upon ATP depletion. In another report (9), HuR and tristetraprolin (TTP) regulated the stability of the transcript encoding the Na+-dependent bile acid transporter.

Immune regulation. Although there is only limited knowledge of HuR functions in a setting of immune-mediated or inflammatory kidney diseases, HuR has been strongly implicated in perpetuating the inflammatory process in general. In various cell types, HuR binds transcripts encoding inflammatory cytokines [IL-6, IL-8, TNF-α, TGF-β, and interferon (IFN)-γ] and inflammation-promoting mediators (COX-2 and inducible NO synthase) and promotes their expression (9). By a different mechanism, HuR downregulates levels of thrombomodulin, which has an anti-inflammatory action. HuR effects are inhibited by anti-inflammatory cytokines such as IL-10 or IL-19, and, in fact, affecting HuR’s ability to stabilize transcripts of proinflammatory cytokines is thought to be one of the major modes of action of these anti-inflammatory factors (82).

Anti-TIA-1/TIAR antibodies were assessed in patients with autoimmune diseases and found in ~61% of patients with systemic lupus (44). Interestingly, autoantibodies against TIAR were associated with systemic lupus erythematosus (SLE) nephritis. In cancer cell lines, TIAR has previously been shown to bind TNF-α and COX-2 and has been implicated in regulating the expression of inducible NO synthase and the β-adrenergic receptor (10, 24, 32, 45). The spectrum of genes regulated by TIAR may suggest a role for TIAR in inflammation and apoptosis control applicable also in the pathogenesis of lupus nephritis.

TIAR has been shown to bind and inhibit the translation of TNF-α mRNA (69). TIAR expression is altered in SLE, and it has been hypothesized that dysregulated expression leads to an increased presence of anti-TIA-1 antibodies in SLE patients. As suggested by epitope mapping, anti-TIA-1 antibodies from SLE patients bind one of the RNA recognition motifs of the
TIA-1 molecule that is critically important for TIA-1 binding of target transcripts (such as the TNF-α gene) to exert its translational inhibitory effect. Therefore, the effect of anti-TIA-1 antibody may be responsible for the lack of TIA-1 inhibitory actions on TNF-α translation and may lead to higher TNF-α levels. In accordance with this finding, the presence of anti-TIA-1 antibodies was related to a more severe course of SLE, elevated anti-double-stranded DNA antibodies, and higher TNF-α levels, although no correlation was found between lupus nephritis and the presence of anti-TIA-1 antibodies (44).

Vascular tone and hypertension. Defects in soluble guanylate cyclase and NO signaling regulating smooth muscle tone has been found in animal models of hypertension (8, 50, 51). HuR has been demonstrated to bind and regulate the expression of soluble guanylate cyclase transcripts α1 and β1. Moreover, the expression of HuR was lower in older hypertensive rats compared with younger rats, likely accounting for the decreased soluble guanylate cyclase levels and worsening of hypertension (50, 51). Hydrogen peroxide treatment as a model of ischemic stress led to an increased stability of soluble guanylate cyclase β1-subunit mRNA by HuR translocation into the cytoplasm and increased transcript binding (58).

On the other hand, increased HuR levels may also contribute to hypertension, as insulin has been shown to upregulate ANG II type 1 (AT1) receptors by increasing the stability of its transcript, thus partially explaining the mechanism of hypertension in diabetes (67). In cultured human vascular smooth muscle cells, HuR has been shown to target several genes responsible for vascular homeostasis and HuR silencing, leading to decreased proliferation of smooth muscle cells (71).

Another TTR-RBP, DJ-1, has also been found to play a role in an animal model of hypertension, as there was a 20% increase in blood pressure in mice with low DJ-1 levels. DJ-1 silencing in proximal tubular cells led to increased levels of prooxidant enzymes and increased ROS production. It has been hypothesized that DJ-1 may regulate this process at the translation control level, but the precise mechanism is not clear (12). The effect of DJ-1 on renal functions may be more complex and extend beyond posttranscriptional regulation, as DJ-1 has also been shown to mediate mesangial cell hypertrophy by stimulating Akt and inducing its phosphorylation in response to high glucose levels without influencing mRNA stability or translation (15).

Both aldosterone and 1-deamino-8-D-arginine vasopressin (dAVP; V2 receptor agonist) regulate the synthesis of α- and γ-epithelial Na+ channel subunits by affecting translation. Several TTR-RBPs [HuR, AU-rich element RNA-binding protein (AUF)-1, and TTP] have been shown to bind the 3′-UTR of these transcripts, but HuR seemed to be the most significant (68).

Acid-base balance. Phosphoenolpyruvate carboxykinase (PEPCK) holds the center stage of gluconeogenesis and ammoniagenesis control in proximal tubular cells (19, 33, 37, 63). PEPCK mRNA harbors several cis instability elements, which are the targets of AUF-1 and HuR proteins (37, 63). Upon cAMP-dependent activation of PKA caused by hormonal stimulation [e.g., parathyroid hormone (PTH)], phosphorylation of AUF-1 ensues the impairment of its ability to interact with target mRNAs leading to stabilization of the PEPCK transcript (19). pH-dependent stabilization of the PEPCK transcript reflects a combinatorial effect between HuR and AUF-1: during physiological, normal pH, both HuR and AUF-1 bind to their cis elements in the 3′-UTR of PEPCK mRNA, and AUF-1 recruits deadenylase, promoting PEPCK degradation at a constant rate. In a state of acidosis, the level of HuR phosphorylation decreases, leading to increased HuR binding, remodeling of the ribonucleoprotein complex, and less effective deadenylase recruitment (33, 63).

Glutaminase is another enzyme in ammoniagenesis, a process that deamidates glutamine in mitochondria, leading to ammonia generation. This enzyme is also regulated in a pH-dependent manner at the posttranscriptional level. It has been hypothesized that at pH 7.4, the 3′-UTR of the transcript is bound by ζ-cryst and/or AUF-1, which promotes its degradation at a constant rate. During acidosis, ζ-cryst gets translocated to stress granules, and the transcript is bound by HuR upon its translocation from the nucleus, which altogether leads to increased glutaminase stability (41, 77, 78).

TTR-RBPs and Their Effect on Anemia of Chronic Disease and Bone Mineral Disease

Kidneys have crucial functions in the regulation of normal erythropoiesis as well as calcium and phosphate homeostasis. Several of the genes central to these processes [such as hypoxia-inducible factor (HIF)-1α in anemia or PTH in bone mineral disease] are regulated at the posttranscriptional level by TTR-RBPs. This section describes the particular mechanisms of regulation.

Bone mineral disease and vascular calcification. Under basal conditions, PTH mRNA levels are regulated by balanced interactions between stabilizing factors (AUF-1 and upstream of N-ras) and a destabilizing factor (KH-type splicing regulatory protein). Hypocalcemia or the presence of chronic kidney disease (CKD) leads to the inactivation of Pin1, a peptidyl-prollyl cis-trans isomerase that specifically binds phosphorylated serine/threonine-proline motifs and catalyzes cis-trans isomerization of the peptide bonds leading to a protein change of function. Decreased Pin1 activity results in KH-type splicing regulatory protein phosphorylation and its inactivation, allowing a greater stabilizing effect of AUF-1 to occur, which leads to increased PTH mRNA stability (52, 65). In the case of PTH, unlike in many other transcripts, AUF-1 seems to be a stabilizing rather than destabilizing factor. This regulation is likely related to chronic changes characteristic of CKD rather than an acute response to calcium concentrations.

Pyrophosphate serves as an inhibitor of calcification in the vascular extracellular matrix. Ankylosing protein homolog (ANKH) controls pyrophosphate efflux from cells to the extracellular matrix, thus regulating vascular calcification. It has been proposed during conditions of chronic inflammation or CKD that high TNF-α levels lead to NF-κB activation and increased TTP function, which, in turn, leads to the destabilization of ANKH mRNA and increased vascular calcification through decreased expression of ANKH (89).

Anemia. Erythropoietin (EPO) expression is regulated by the transcription factor HIF-1, but the posttranscriptional regulation of the EPO transcript itself has been reported as well (29). The 3′-UTR of the EPO transcript is bound by a TTR-RBP called EPO RNA-binding protein, whose levels went up under hypoxic conditions. EPO RNA-binding protein has been dem-
onstrated to stabilize EPO mRNA in normoxic cells, but more so in hypoxia (60, 74).

In an animal model of CKD, HIF-1 induction improves renal hemodynamics, promotes renal cell growth, and stimulates angiogenesis (17). Probably the best-described regulation of HIF-1 is at the posttranslational level, when HIF-1α undergoes von Hippel-Lindau-mediated degradation after hydroxylation at prolyl residues. At the posttranscriptional level, HuR has been shown to bind HIF-1α mRNA transcript in androgen-treated prostate cancer cells as well as in HeLa cells (28, 79). HuR has been shown to cooperate with polyypyrimidine tract-binding protein, which is another TTR-RBP, and the simultaneous binding of the two TTR-RBPs on multiple sites of the HIF-1α transcript together promote HIF-1α translation (28). In a separate study, polyypyrimidine tract-binding protein binding to the polyypyrimidine tract present in the 5′-UTR of HIF-1α mRNA promoted its translation during hypoxic treatment independent of HuR, which was demonstrated in HEK-293 cells (76).

Iron regulatory proteins are TTR-RBPs involved in the cellular response to hypoxia. In HEK-293 cells, levels of Iron regulatory proteins were upregulated after hypoxia associated with changes in RNA-binding activity (38). In normoxemia, decreased iron availability results in the inhibition of HIF-1α degradation. HIF-1α harbors iron-responsive elements, although whether this interaction regulates HIF-1α expression in hypoxia and iron deficiency is not known (54, 90).

An additional TTR-RBP, cytoplasmic polyadenylation element-binding protein, is associated with HIF-1α mRNA and has been shown to increase HIF-1α translation upon insulin treatment, although it is not known whether this effect is the same in renal tissues and without insulin stimulation (36).

Implications in Aging

As the most common renal diseases caused by atherosclerosis, hypertension, and diabetes are more prevalent in the older population, aging and its relation to kidney have become significant issues in nephrology. In a systemic evaluation of four TTR-RBPs (HuR, AUF-1, TIA-1, and TTP), it was shown that HuR and AUF-1 were moderately expressed in the kidneys compared with other organs and that expression went mildly up with age (59). Unlike HuR and AUF-1, the relative intensity of TIA-1 kidney expression declined with advancing age. Similar to TIA-1, the level of TTP expression was highest in the fetal group and decreased with age (59).

Animal Models

Certain TTR-RBPs are embryonic lethal (such as HuR), which made their initial studies on renal functions difficult. However, other RNA-binding protein knockout models have shown the role of TTR-RBPs in the pathogenesis of renal diseases and embryonic development.

TTP-deficient mice have a phenotype of dermatitis, erosive arthritis, autoimmunity, glomerular mesangial thickening, presence of anti-double-stranded DNA antibodies, antinuclear antibody positivity, and myeloid hyperplasia (84).

The phenotype of RNA-binding protein bicaudal C (Bicc1) mutant mice (Bicc1−/− mice) resembles a polycystic kidney disease (Pkd) phenotype (57). It has been demonstrated that Bicc1 regulates the stability of the Pkd2 mRNA transcript and its translation efficiency by antagonizing the inhibitory activity of the miRNA-17 family on Pkd2 mRNA (85).

Studies in AUF-1 knockout mice have shown that this protein promotes telomerase expression, decreases cellular senescence, and maintains normal aging. AUF-1 does so by binding and activating the promoter for the telomerase catalytic subunit Tert (70). AUF-1 promotes the decay of inflammatory cytokines and destabilization of cell cycle checkpoint genes affecting senescence (56). As aging increases the risk for kidney disease, this may be another mechanism of how AUF-1 influences renal function.

Perspective

Current data obtained so far demonstrate that TTR-RBPs have a broad effect on posttranscriptional regulation in renal physiology and pathology. There are numerous areas where TTR-RBP research can be advanced and help with new, kidney-specific diagnostics and therapy. Technological achievements, such as advancements in technologies of transgenic animals or the advent of so-called photactivatable-ribonucleoside-enhanced cross linking and immunoprecipitation, a method for transcriptome-wide identification of binding sites of RNA-binding proteins, will be invaluable towards this end (35).

For several renal diseases, we are only able to extrapolate certain functions of TTR-RBPs from related yet not renal-specific conditions. An example is the role of HuR in apoptosis/survival of tubular cells during ischemic conditions. We know that HuR is predominantly an antiapoptotic molecule according to the research done on other nonrenal cell lines, but it remains to be determined whether there are different HuR targets and/or different ratios of previously defined proapoptotic versus antiapoptotic targets upon ischemic stimuli.

With the recent boom of knowledge on miRNAs and long noncoding RNAs, it is also becoming apparent that these regulator RNAs interact directly or indirectly with TTR-RBPs to exert their functions, although these experiments have not yet been carried out in kidney-derived cells. TTR-RBPs also regulate the synthesis of certain miRNAs (such as HuR and miRNA-16), probably at the level of splicing (53). It has also been speculated that certain TTR-RBPs (e.g., HuR) can serve as a sponge, sequestering regulatory miRNAs. Collectively, these data suggest that research on TTR-RBPs may also help to elucidate the mechanisms of action of regulatory RNAs. With specific miRNAs involved in renal physiology, the involvement of particular TTR-RBPs can be anticipated.

Surprisingly, there is only a limited amount of data on the actions of TTR-RBPs in many human renal diseases. It would be interesting to see a pattern of expression of TTR-RBPs and their targets in such cases, for example, in glomerular diseases. Dysregulation of immunity is usually under tight control at the posttranscriptional level. Defining a TTR-RBP expression pattern and defining their mRNA targets under such conditions may delineate disease-specific immunoregulatory genes. This may also be true for aging, as atherosclerosis, hypertension, and diabetes are more prevalent with increasing age. The expression pattern of TTR-RBPs is clearly different in young versus old individuals as far as kidneys are concerned, and defining the differentially expressed targets may shed more light on the pathogenesis of these diseases (59).
We currently have only limited knowledge on naturally occurring gene variants of these TTR-RBPs under disease conditions. It remains to be determined how prevalent mutations in the regulatory sequences of these genes are and whether they have effects on dysregulated TTR-RBP expression under adaptive responses in renal diseases.

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