REVIEW ARTICLE

RNA-binding proteins in diabetic microangiopathy

Chao Tu | Liangzhi Wang | Lan Wei

Department of Internal Medicine, The
Third Affiliated Hospital of Soochow
University, Changzhou, China

Correspondence
Lan Wei, Department of Internal
Medicine, The Third Affiliated Hospital
of Soochow University, 185 Juqian Road,
Changzhou, Jiangsu 213000, China.
Email: weilan06082021@163.com

Abstract

Background: As the most common complication of diabetes, the diabetic microangiopathy characterizes diabetic retinopathy (DR) and nephropathy (DN). Diabetic microangiopathy has always been a serious clinical problem. A wide variety of nucleic acid interacting factors called the RNA binding proteins (RBPS) take part in several crucial cellular processes.

Methods: Over the past decade, studies have shown that RBPs have crucial part in both malignant tumors and diabetes, especially in diabetic microangiopathy. This review examined the research history of RBPS in DR and DN.

Results: We reviewed the literature and found that RBPS is potentially useful as therapeutic targets, diagnostic markers, or predict disease progression.

Conclusion: HuR acts as a vital therapeutic targeting protein in diabetic microangiopathy. IGF2BP2, P311, TTP, YBX1, and MBNL1 have a potential role in the treatment of DN.

KEYWORDS
diabetic nephropathy, diabetic retinopathy, non-coding RNA, RNA-binding proteins

1 | INTRODUCTION

Dynamic RNPs (ribonucleoprotein particles) are formed when RNA-binding proteins assemble with RNA. RNP compositions vary depending on the maturation or the functional state of the RNA as well as the cell environment.[1–3] All aspects of RNA life, including splicing, transcription, intracellular trafficking, modification, translation, as well as decay, are regulated by RBPs. In turn, RNA can modulate the location or activity of RBPs through a process called "riboregulation."[4]

The PRK (protein kinase R) induces autophosphorylation and dimerization of proteins through their binding to double-stranded RNA, which activates the enzyme and is a prime example of riboregulation (Figure 1).[5] RBP dysfunction and dysregulation are correlated to several muscular atrophies and neurological disorder diseases in humans, like amyotrophic lateral sclerosis,[6] cancer,[7] and genetic abnormalities.[8]

RBPs are conserved evolutionarily and have a wide distribution in tissues, in line with their common roles concerning housekeeping. In spite of these attributes, alterations or mutations in RBPs responsible for housekeeping can often lead to specific tissue defects. How does this occur? First, RBPs possibly act on their RNA targets or regulatory partners that express tissue specificity. Secondly, RBPs may attach to RNA targets with various specificities and affinities, regulated by modifications in RNA post-translation, their interactions, and local structure or sequence, causing regulatory complex formation to specific cell types.[9–12] Third, attachment of RNA by itself may not always lead to regulatory effects. Even though RBPs are capable of binding hundreds of RNA targets, only some of them are regulated in particular cellular conditions. In RNA regulons, a set of RNAs are coordinated and regulated by a given RBP under the influence of stimuli.[13,14] Finally, the RBPs cause the formation of extensive network structures with their RNA targets and other
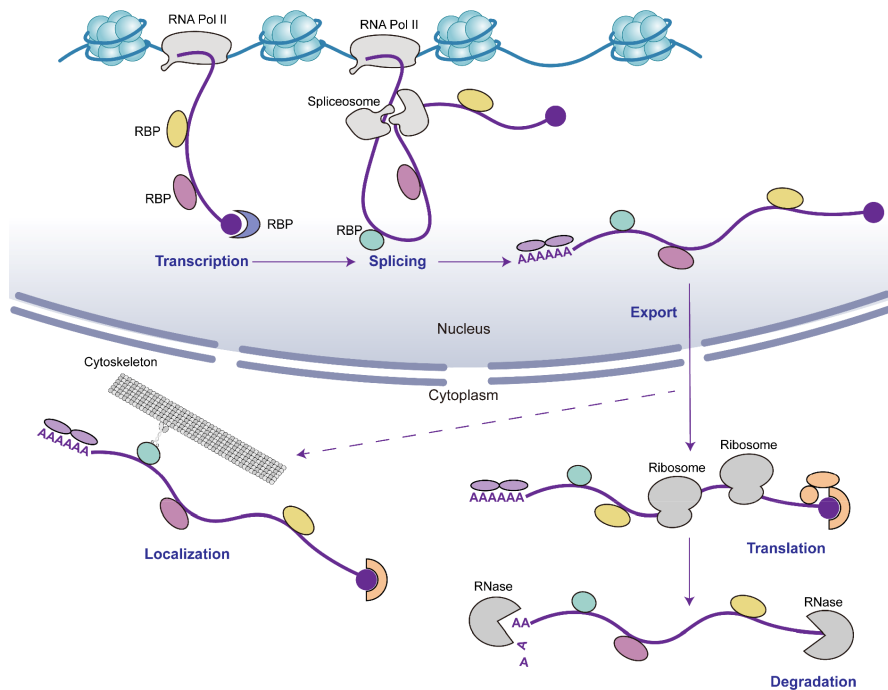
FIGURE 1 Several different ways of RNA-binding proteins regulating RNAs (polyadenylation, transcription, capping, splicing)

proteins, which may provide robustness so that alterations can be differentially buffered in one cell type versus another.

A lack of simple suitable methods has long hampered the systematic characterization of the interactions between RNA and proteins in contrast to protein–protein interactions. RBPs were therefore not at the forefront of medicine or molecular biological studies. In the past decade, however, high-throughput techniques for identifying RBPs were developed, such as RIC (RNA interactome capture)[15–17] and RNA target transcript analysis using CLIP (cross-linking and immunoprecipitation).[18–22] In combination with RNA sequencing, CLIP has revolutionized the existing knowledge on RBPs. In 2020, studies on RNA interactome were published in a comprehensive database, facilitating the analysis of the available datasets.[23]

RBPs may play a significant role in renal diseases, like AKI (acute kidney injury),[24] PKD (polycystic kidney disease),[25] and LN (lupus nephritis).[26] Therefore, the modulation of the events related to the binding of RNA and proteins may provide openings for new therapies in renal diseases. RBP appears to be studied in greater depth in diabetic nephropathy (DN). Our search reveals that there have been many studies on RBP molecules relevant to diabetic retinopathy (DR) of diabetic microvascular disease. We present a current review of the knowledge on RBPs, their interactions with non-coding RNA (ncRNA), mRNA, proteins, their function in microvascular disease in diabetes, and prospect as new therapeutic targets.

2 | RBPs IN DIABETIC RETINOPATHY

2.1 | Human antigen R (HuR)

During 2007, researchers exposed cells on bovine retinal pericytes to 30 mM glucose for 15 min to form a model of retinal blood glucose injury. During this process, the soluble protein kinase C (PKC) βII was

found to move to the membrane, and HuR protein levels increased in the cytoskeleton.[27] Because PKC is a serine–threonine kinase, further research revealed that HuR is phosphorylated in serine but not in threonine. Based on immunoprecipitation and real-time PCR, there was an increased binding between HuR and VEGF (vascular endothelial growth factor) mRNA within the mRNP compartment. In recent studies, it has been shown that VEGF plays an important role in diabetic retinopathy.[28,29] The PKC/HuR/VEGF axis represents an important route to develop diabetic retinopathy in the future. In a recent study, we compared the best-scored compounds in diabetic retinopathy in vitro model, specifically hRECs (human retinal endothelial cells) exposed to high glucose (25 mM). In our study, the authors found that two indole derivatives, VP12/110 and VP12/14, modulated the expression of HuR and impeded the release of TNF- α and VEGF in HREC exposed to HG (high glucose). In this cell model, HUR expression could be inhibited by VP12/14 and VP12/110. They also found that VP12/110 and VP12/14 modulated the levels of VEGFA mRNA and exhibited antiangiogenic effects. Thus, combined with previous research, HUR binds directly to the mRNA of VEGF and VP12/14, and VP12/110 can be considered HUR inhibitors and are of therapeutic value in diabetic retinopathy.[30]

2.2 | The lin-28 homolog B (LIN28B)

Studies have indicated that the consistent expression of LIN28B (lin-28 homolog B), a member of the highly conserved family of RNA-binding proteins, enhances the production of VEGF.[31] According to Fu et al.,[32] mir-152 can directly bind to and inhibit the expression of LIN28B. Mir-152 may also inhibit the angiogenic ability of hRECs and hRMECs (retinal microvascular endothelial cells). Mir-152 regulates angiogenesis by inhibiting the expression of lin28B, thereby regulating VEGF expression (Figure 2).

3 | RBPs IN DIABETIC NEPHROPATHY

3.1 | RNA-binding protein regulatory subunit (#38)

Early studies using MS-MALDI and 2-D gel electrophoresis analysis found that expression of #38 was significantly increased in DN.[33] RNA-binding protein regulatory subunit 38, also known as Protein DJ-1, is likely to be significantly more abundant in T1DM patients with DN due to specific mRNAs stabilization, a process by which cells may control protein expression levels.[34] Associations have been observed between three RNA-binding proteins and insulin resistance; therefore, increased type 2 diabetes risk.[35,36] Hence, the authors hypothesized an association between elevated RNA-binding protein subunit (#38) levels and diabetic renal complications in T1DM patients with DN.[37]

3.2 | Insulin-like growth factor mRNA-binding protein 2 (IGF2BP2)

Diabetes type 2 and DKD risk increase with single-nucleotide polymorphisms in the gene coding for IGF2BP2.[38,39] In cultured podocytes, IGF2BP2 is bound to mRNA of the LAMB2 (basement membrane component laminin- β 2), triggering its translocation to the cytoskeleton of actin, where its translation into protein200 occurs. Let-7b miRNA induction, however, decreases IGF2BP2 and LAMB2 expression under high-glucose conditions by repressing the HMGA2, which encodes the transcription factor HMGAT2.[40] IGF2-BP2 levels, LAMB2 levels, and HMGA2 levels decrease in the glomeruli of DN rats as well. Additionally, the anti-sense lncRNA for AIRN (IGF2R non-protein-coding RNA) has been identified as a key regulator of IGF2BP2 protein stability and podocyte and glomerular basement membrane integrity.[41] HG-treated podocytes and DN in mice reduced AIRN expression, leading to podocyte apoptosis. Conversely, overexpression of AIRN increased the survival of podocytes by stabilizing IGF2BP2. Podocytes stimulated with HG exhibited decreased IGF2BP2 and AIRN levels, and IGF2BP2 and its downstream targets were restored when AIRN was overexpressed, resulting in the viability of podocytes and integrity of the glomerular basement membrane.

3.3 | Y-box-binding protein 1(YBX1)

YBX1 transcript and protein levels were reduced in glomeruli of both type 1 (streptozotocin-induced) and type 2 (db/db) diabetes mellitus mice models.[42] MiR-216a, with enhanced expression in mice with diabetes and mouse mesangial cells treated with TGFβ, exhibited negatively regulated YBX1. In untreated mouse mesangial cells, YBX1 accumulated in processing bodies, could bind to TSC22 (TGFβ-stimulated clone 22), and promote the ECM protein COL1A2 (collagen type Iα-2).[43] By stimulating TGFβ, the binding of YBX1 to TSC22 mRNA was inhibited, resulting in higher expression levels of TSC22 and COL1A2 proteins in mouse mesangial cells.

3.4 | Muscleblind-like splicing regulator 1 (MBNL1)

When metformin is administered to diabetic mice, levels of MBNL1 increase.[44] Metformin treatment of renal epithelial tubular cells and HG-treated HK2 cells from diabetic mice restored the expression of MBNL1 protein and allowed it to attach and stabilize miRNA miR-130a-3p, a transcription factor that negatively regulates STAT3 (signal transducer and activator of transcription 3). This reduced the aging of cells. In DKD, there appears to be an accumulation of senescent cells in the tubules and glomeruli, cells which play a significant non-autonomous part in the disease development due to their secretory phenotype. Therefore, understanding the MBNL1–miR-130a-3p–STAT3 axis may lead to new treatment opportunities for DKD patients.[45]
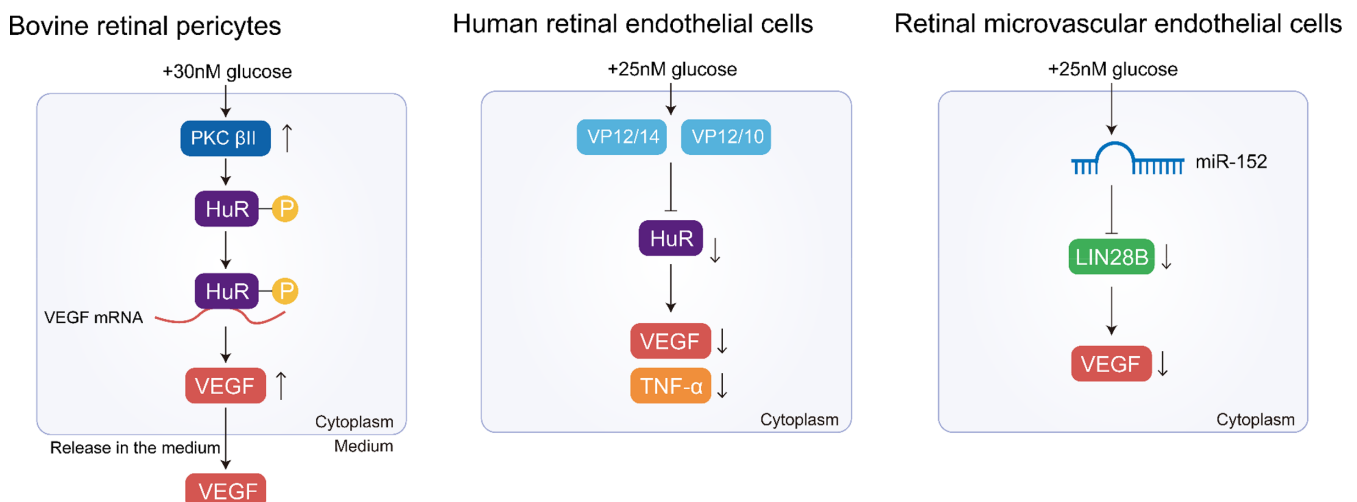

FIGURE 2 The mechanism of RNA-binding proteins in three sorts of high glucose induced retinal cells (bovine retinal pericytes, human retinal endothelial cells, human retinal microvascular endothelial cells)

3.5 | Neuronal regeneration-related protein (P311)

Furthermore, TGFβ activator P311 is also linked to kidney fibrosis in DKD.[46] Despite renal dysfunction and accumulation of mesangial ECM in mice with diabetes, butyrate administration alleviated these conditions via the miR-7a-5p-mediated suppression of P311 expression and TGFβ downregulation. Furthermore, miR-7a-5p overexpression protected diabetic mice against the dysfunction and fibrosis of the kidneys.

3.6 | Human antigen R (HuR)

DKD results in elevated levels of HuR expression in the tubular epithelial cells of rat and human kidneys and is correlated with elevated EMT markers compared to healthy controls.[47] In response to HG concentrations, the HuR plies from the cytoplasm to the nucleus. Hg-induced EMT in HK2 cells was reduced when HuR was silenced. Studies that showed a positive correlation between increased HuR expression, activation of Nlrp3 (NACHT, LRR, and PYD domain-containing protein 3) inflammasome, and pyroptosis in epithelial cells of renal tubules from rats with diabetes and HG-treated HK2 cells provide further evidence of HuR's role in DKD.[48,49] In addition, this work identified another mode of regulation of HuR expression post-transcriptionally, which involves inhibition of HuR expression by miR-23c, which targets the lung cancer lncRNA MALAT1. HK2 cells were induced to upregulate MALAT1, HuR, and various NLRP3 inflammasome components under hyperglycemic conditions, while miR-23c was downregulated. Based on the researchers' hypothesis, MALAT1 sequesters miR-23c and prevents suppression of HuR by miR-23c, increasing pyroptosis. Inflammasomes are important sensors of the innate immune system, but NOD (nucleotide-binding oligomerization domain-containing)-like receptors (NLRs) play a significant role in DKD.[50] Increased NOD2 levels were observed to associate with increased abundance of HuR and proteinuria in DKD patients' and diabetic rats'

kidneys.[51] Moreover, HG-induced mesangial cells upregulated NOD2 and HuR, attributed to HuR nucleocytoplasmic shuttling and NOD2 mRNA post-transcriptional stabilization. Moreover, HuR silencing improved kidney damage in rats with diabetes. In HG-stimulated mesangial cells and rats with diabetes, NOX4 (NADPH oxidase 4) levels were also elevated. Researchers suggest that hyperglycemia induces NOX4, resulting in increased ROS levels and cytoplasmic transportation of HuR, facilitating NOD2 mRNA stabilization by HuR. Furthermore, HuR was shown to attach to NOX4 mRNA and stabilize it in HG-treated mesangial cells and rats with diabetes,[52] indicating a positive feedback loop between HuR and NOX4. In a subsequent study, an abundance of HuR was also shown to correlate with podocyte injury and inflammation in diabetic mice that confirmed increased levels of HuR in patients with diabetes.[53]

3.7 | Tristetraprolin (TTP)

TTP is an adenosine and uridine rich elements-RNA binding protein (RBP) that induces the decay of mRNA and represses the translation of its targets.[54] The RBP that participates in the decay and destabilization of TNF (tumor necrosis factor) mRNA is an important anti-inflammatory mediator.[55] Reduced TTP expression is directly associated with decreased expression of IL-8 and IL-6 in patients with diabetes and proteinuria.[56] In patients with DKD, TTP levels are negatively associated with miR-29c.[57] Mouse podocytes treated with HG-induced the expression of miR-29c repressed TTP translation and increased TNF and IL-6 levels, suggesting TTP as a direct target of translational repression mediated by miR-29c. A mouse model of the doxorubicin-induced nephrotic syndrome also exhibited decreased levels of TTP; activated signaling of IL-13–STAT6; and increased levels of IL-1β, IL-6, and TNF.[58] Furthermore, doxorubicin-treated HK2 cells had reduced levels of TTP, while TTP overexpression in the cells treated with doxorubicin had reduced expression of factors associated with oxidative stress, inflammation, and apoptosis (Figure 3). The main research
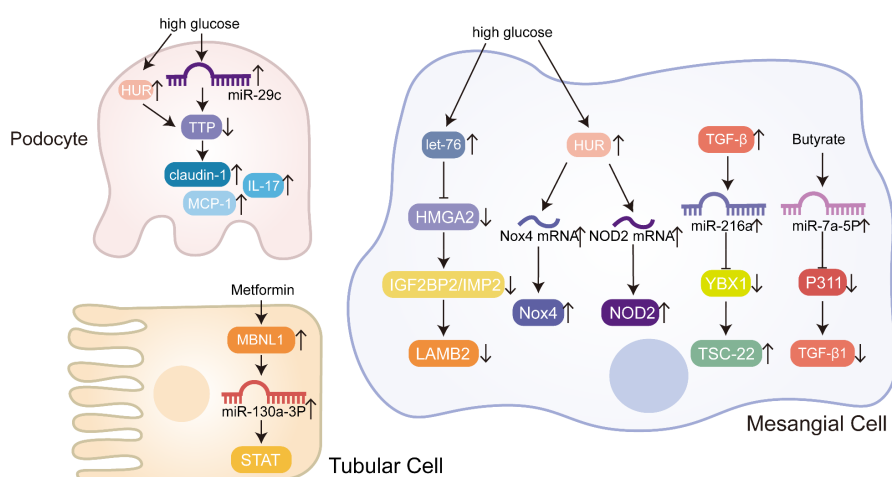

FIGURE 3 The mechanism of RNA-binding proteins in kidney cells by high glucose inducing or under the function of drugs

TABLE 1 RBPs in this review and their mechanisms in diabetic microangiopathy

Molecules of RBPS	Effects on diabetic microangiopathy	Mechanism	References
HuR	Exacerbate diabetic retinopathy	Binds and elevates VEGF mRNA expression	27
HuR	Exacerbate diabetic retinopathy	VP12/14 and VP12/110 modulate HuR expression	30
LIN28B	Exacerbate diabetic retinopathy	miR-152 downregulates LIN28B expression	32
IGF2BP2	Exacerbate diabetic nephropathy	IGF2BP2/IMP2 regulates the expression of Lamb2 mRNA	40
Ybx1	Alleviate diabetic nephropathy	Post-transcriptional upregulation of Tsc-22 by Ybx1, a target of miR-216a	42
MBNL1	Alleviate diabetic nephropathy	Metformin regulates MBNL1/miR-130a- 3p/STAT3 pathway	44
P311	Exacerbate diabetic nephropathy	Butyrate regulation miR-7a-5p/P311/TGF-β1 pathway	46
HuR	Exacerbate diabetic nephropathy	HuR upregulates NOD2 mRNA expression	51
HuR	Exacerbate diabetic nephropathy	HuR upregulates NOX4 mRNA expression	52
TTP	Alleviate diabetic nephropathy	TTP modulated mRNA and protein levels of IL-17 and claudin-1	53

molecules and mechanisms reviewed above are summarized in Table 1.

4 | CONCLUSIONS

RBPs are involved in pathologies of glomeruli and kidney tubules, given the central role they play in RNA metabolism and cell biology, and may be involved in diabetic microangiopathy. It is only recently that this field has been gaining attention in studies on nephrology, so there are likely to be many discoveries. Microangiopathy is one of many disorders where understanding how RNA interacts with proteins can provide new therapeutic options as well as improve understanding of the disease. Using new techniques to capture RBPs as well as their target RNAs, this therapeutic potential would provide an unprecedented opportunity for microangiopathy research. In the field of DR, research has been relatively scarce, which leaves plenty of room for future study. A significant potential target for treating diabetic microangiopathy appears to be RBPS.

CONFLICT OF INTERESTS
Authors declare there is no conflict of interest.

AUTHOR CONTRIBUTIONS
Chao Tu and Liangzhi Wang contributed to the writing of the manuscript. Lan Wei conceived and finalized the content of the manuscript. All authors reviewed, contributed to the revisions, and finalized the drafts.

CONSENT FOR PUBLICATION
All authors agree to publish this article.

DATA AVAILABILITY STATEMENT
The datasets generated in the current study will be made available on request by the corresponding author.

ORCID
Lan Wei https://orcid.org/0000-0003-0673-725X

REFERENCES
1. Mitchell SF, Parker R. Principles and properties of eukaryotic mRNPs. *Mol Cell*. 2014;54:547-558.
2. Gerstberger S, Hafner M, Tuschl T. A census of human RNA-binding proteins. *Nat Rev Genet*. 2014;15:829-845.
3. Singh G, Pratt G, Yeo GW, et al. The clothes make the mRNA: past and present trends in mRNP fashion. *Annu Rev Biochem*. 2015;84:325-354.
4. Hentze MW, Castello A, Schwarzl T, et al. A brave new world of RNA-binding proteins. *Nat Rev Mol Cell Biol*. 2018;19:327-341.
5. Bou-Nader C, Gordon JM, Henderson FE, et al. The search for a PKR code-differential regulation of protein kinase R activity by diverse RNA and protein regulators. *RNA*. 2019;25:539-556.
6. Kapeli K, Martinez FJ, Yeo GW. Genetic mutations in RNA-binding proteins and their roles in ALS. *Hum Genet*. 2017;136:1193-1214.
7. Lukong KE, Chang K-W, Khandjian EW, et al. RNA-binding proteins in human genetic disease. *Trends Genet*. 2008;24:416-425.
8. Gebauer F, Schwarzl T, Valcárcel J, et al. RNA-binding proteins in human genetic disease. *Nat Rev Genet*. 2021;22:185-198.
9. Piqué M, López JM, Foissac S, et al. A combinatorial code for CPE-mediated translational control. *Cell*. 2008;132:434-448.
10. Iadevaia V, Gerber AP. Combinatorial control of mRNA fates by RNA-binding proteins and non-coding RNAs. *Biomolecules*. 2015;5:2207-2222.
11. Achsel T, Bagni C. Cooperativity in RNA-protein interactions: the complex is more than the sum of its partners. *Curr Opin Neurobiol*. 2016;39:146-151.
12. Beckmann BM, Castello A, Medenbach J. The expanding universe of ribonucleoproteins: of novel RNA-binding proteins and unconventional interactions. *Pflugers Arch*. 2016;468:1029-1040.
13. Morris AR, Mukherjee N, Keene JD. Systematic analysis of post-transcriptional gene expression. *Wiley Interdiscip Rev Syst Biol Med*. 2010;2:162-180.

14. Imig J, Kanitz A, Gerber AP. RNA regulons and the RNA-protein interaction network. *Biomol Concepts*. 2012;3:403-414.

15. Baltz A, Munschauer M, Schwanhäusser B, et al. The mRNA-bound proteome and its global occupancy profile on protein-coding transcripts. *Mol Cell*. 2012;46:674-690.

16. Castello A, Fischer B, Eichelbaum K, et al. Insights into RNA biology from an atlas of mammalian mRNA-binding proteins. *Cell*. 2012;149:1393-1406.

17. Conrad T, Albrecht A-S, de Melo Costa VR, et al. Serial interactome capture of the human cell nucleus. *Nat Commun*. 2016;7:11212.

18. Licatalosi DD, Mele A, Fak JJ, et al. HITS-CLIP yields genome-wide insights into brain alternative RNA processing. *Nature*. 2008;456:464-469.

19. Hafner M, Landthaler M, Burger L, et al. Transcriptome-wide identification of RNA-binding protein and microRNA target sites by PAR-CLIP. *Cell*. 2010;141:129-141.

20. König J, Zarnack K, Rot G, et al. iCLIP reveals the function of hnRNP particles in splicing at individual nucleotide resolution. *Nat Struct Mol Biol*. 2010;17:909-915.

21. Van Nostrand EL, Pratt GA, Shishkin AA, et al. Robust transcriptome-wide discovery of RNA-binding protein binding sites with enhanced CLIP (eCLIP). *Nat Methods*. 2016;13:508-514.

22. Sharma D, Zagore LL, Brister MM, et al. The kinetic landscape of an RNA-binding protein in cells. *Nature*. 2021;591:152-156.

23. Caudron-Herger M, Jansen RE, Wassmer E, et al. RBP2GO: a comprehensive pan-species database on RNA-binding proteins, their interactions and functions. *Nucleic Acids Res*. 2021;49:D425-D436.

24. Cen C, Yang W-L, Yen H-T, et al. Deficiency of cold-inducible ribonucleic acid-binding protein reduces renal injury after ischemia-reperfusion. *Surgery*. 2016;160:473-483.

25. Piazzon N, Maisonneuve C, Guilleret I, et al. Bicc1 links the regulation of cAMP signaling in polycystic kidneys to microRNA-induced gene silencing. *J Mol Cell Biol*. 2012;4:398-408.

26. Katsuyama T, Li H, Comte D, et al. Splicing factor SRSF1 controls T cell hyperactivity and systemic autoimmunity. *J Clin Invest*. 2019;129:5411-5423.

27. Amadio M, Scapagnini G, Lupo G, et al. PKCbetaII/HuR/VEGF: a new molecular cascade in retinal pericytes for the regulation of VEGF gene expression. *Pharmacol Res*. 2008;57:60-66.

28. Ji L, Tian H, Webster KA, et al. Neurovascular regulation in diabetic retinopathy and emerging therapies. *Cell Mol Life Sci*. 2021;78:5977-5985.

29. Mahdy RA, Nada WM, Hadhoud KM, et al. The role of vascular endothelial growth factor in the progression of diabetic vascular complications. *Eye*. 2010;24:1576-1584.

30. Platania CBM, Pittalà V, Pascale A, et al. Novel indole derivatives targeting HuR-mRNA complex to counteract high glucose damage in retinal endothelial cells. *Biochem Pharmacol*. 2020;175:113908.

31. Wu T, Jia J, Xiong X, et al. Increased expression of Lin28B associates with poor prognosis in patients with oral squamous cell carcinoma. *PLoS One*. 2013;8:e83869.

32. Fu X, Ou B. miR-152/LIN28B axis modulates high-glucose-induced angiogenesis in human retinal endothelial cells via VEGF signaling. *J Cell Biochem*. 2020;121:954-962.

33. Tessari P, Puricelli L, Iori E, et al. Altered chaperone and protein turnover regulators expression in cultured skin fibroblasts from type 1 diabetes mellitus with nephropathy. *J Proteome Res*. 2007;6:976-986.

34. Carballo E, Lai WS, Blackshear PJ. Feedback inhibition of macrophage tumor necrosis factor-alpha production by tristetraprolin. *Science*. 1998;281:1001-1005.

35. Wilhelmi I, Neumann A, Jähnert M, et al. Enriched alternative splicing in islets of diabetes-susceptible mice. *Int J Mol Sci*. 2021;22(16):8597.

36. Si R, Cabrera JTO, Tsuji-Hosokawa A, et al. HuR/Cx40 downregulation causes coronary microvascular dysfunction in type 2 diabetes. *JCI Insight*. 2021;6(21):e147982.

37. Good AL, Stoffers DA. Stress-induced translational regulation mediated by RNA binding proteins: key links to beta-cell failure in diabetes. *Diabetes*. 2020;69:499-507.

38. Christiansen J, Kolte AM, Hansen TVO, et al. IGF2 mRNA-binding protein 2: biological function and putative role in type 2 diabetes. *J Mol Endocrinol*. 2009;43:187-195.

39. Gu T, Horová E, Möllsten A, et al. IGF2BP2 and IGF2 genetic effects in diabetes and diabetic nephropathy. *J Diabetes Complications*. 2012;26:393-398.

40. Schaeffer V, Hansen KM, Morris DR, et al. RNA-binding protein IGF2BP2/IMP2 is required for laminin-beta2 mRNA translation and is modulated by glucose concentration. *Am J Physiol Renal Physiol*. 2012;303:F75-F82.

41. Jing F, Zhao J, Jing X, et al. Long noncoding RNA Airn protects podocytes from diabetic nephropathy lesions via binding to Igf2bp2 and facilitating translation of Igf2 and Lamb2. *Cell Biol Int*. 2020;44:1860-1869.

42. Kato M, Wang L, Putta S, et al. Post-transcriptional up-regulation of Tsc-22 by Ybx1, a target of miR-216a, mediates TGF-{beta}-induced collagen expression in kidney cells. *J Biol Chem*. 2010;285:34004-34015.

43. Murugesan SN, Yadav BS, Maurya PK, et al. Expression and network analysis of YBX1 interactors for identification of new drug targets in lung adenocarcinoma. *J Genomics*. 2018;6:103-112.

44. Jiang X, Ruan X-L, Xue Y-X, et al. Metformin reduces the senescence of renal tubular epithelial cells in diabetic nephropathy via the MBNL1/miR-130a-3p/STAT3 pathway. *Oxid Med Cell Longev*. 2020;2020:8708236.

45. Wiley CD. Role of senescent renal cells in pathophysiology of diabetic kidney disease. *Curr Diab Rep*. 2020;20:33.

46. Du Y, Yang YT, Tang G, et al. Butyrate alleviates diabetic kidney disease by mediating the miR-7a-5p/P311/TGF-beta1 pathway. *FASEB J*. 2020;34:10462-10475.

47. Yu C, Xin W, Zhen J, et al. Human antigen R mediated post-transcriptional regulation of epithelial-mesenchymal transition related genes in diabetic nephropathy. *J Diabetes*. 2015;7:562-572.

48. Li X, Zeng LI, Cao C, et al. Long noncoding RNA MALAT1 regulates renal tubular epithelial pyroptosis by modulated miR-23c targeting of ELAVL1 in diabetic nephropathy. *Exp Cell Res*. 2017;350:327-335.

49. Shahzad K, Bock F, Dong W, et al. Nlrp3-inflammasome activation in non-myeloid-derived cells aggravates diabetic nephropathy. *Kidney Int*. 2015;87:74-84.

50. Du P, Fan B, Han H, et al. NOD2 promotes renal injury by exacerbating inflammation and podocyte insulin resistance in diabetic nephropathy. *Kidney Int*. 2013;84:265-276.

51. Shang J, Wan Q, Wang X, et al. Identification of NOD2 as a novel target of RNA-binding protein HuR: evidence from NADPH oxidase-mediated HuR signaling in diabetic nephropathy. *Free Radic Biol Med*. 2015;79:217-227.

52. Shi Q, Lee D-Y, Féliers D, et al. Interplay between RNA-binding protein HuR and Nox4 as a novel therapeutic target in diabetic kidney disease. *Mol Metab*. 2020;36:100968.

53. Guo J, Lei M, Cheng F, et al. RNA-binding proteins tristetraprolin and human antigen R are novel modulators of podocyte injury in diabetic kidney disease. *Cell Death Dis*. 2020;11:413.

54. Brooks SA, Blackshear PJ. Tristetraprolin (TTP): interactions with mRNA and proteins, and current thoughts on mechanisms of action. *Biochim Biophys Acta*. 2013;1829:666-679.

55. Taylor GA, Carballo E, Lee DM, et al. A pathogenetic role for TNF alpha in the syndrome of cachexia, arthritis, and autoimmunity resulting from tristetraprolin (TTP) deficiency. *Immunity*. 1996;4:445-454.

56. Liu F, Guo J, Zhang Q, et al. The expression of tristetraprolin and its relationship with urinary proteins in patients with diabetic nephropathy. *PLoS One*. 2015;10:e0141471.

57. Guo J, Li J, Zhao J, et al. MiRNA-29c regulates the expression of inflammatory cytokines in diabetic nephropathy by targeting tristetraprolin. *Sci Rep*. 2017;7:2314.

58. Zhang Q, Wu G, Guo S, et al. Effects of tristetraprolin on doxorubicin (adriamycin)-induced experimental kidney injury through inhibiting IL-13/STAT6 signal pathway. *Am J Transl Res*. 2020;12:1203-1221.