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Emerging roles of RNA binding proteins in diabetes and their therapeutic potential in diabetic complications

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Abstract

Diabetes is a debilitating health care problem affecting 422 million people around the world. Diabetic patients suffer from multi-systemic complications that can cause mortality and morbidity. Recent advancements in high throughput next generation RNA-sequencing and computational algorithms led to the discovery of aberrant post-transcriptional gene regulatory programs in diabetes. However, very little is known about how these regulatory programs are mis-regulated in diabetes. RNA-binding proteins (RBPs) are important regulators of post-transcriptional RNA networks, which are also dysregulated in diabetes. Human genetic studies provide new evidence that polymorphisms and mutations in RBPs are linked to diabetes. Therefore, we will discuss the emerging roles of RBPs in abnormal post-transcriptional gene expression in diabetes. Questions that will be addressed are: Which post-transcriptional mechanisms are disrupted in diabetes? Which RBPs are responsible for such changes under diabetic conditions? How are RBPs altered in diabetes? How does dysregulation of RBPs contribute to diabetes? Can we target RBPs using RNA-based methods to restore gene expression profiles in diabetic patients? Studying the evolving roles of RBPs in diabetes is critical not only for a comprehensive understanding of diabetes pathogenesis, but also to design RNA-based therapeutic approaches for diabetic complications.

Graphical/Visual Abstract

Role of RNA binding proteins in development of diabetes and diabetic complications

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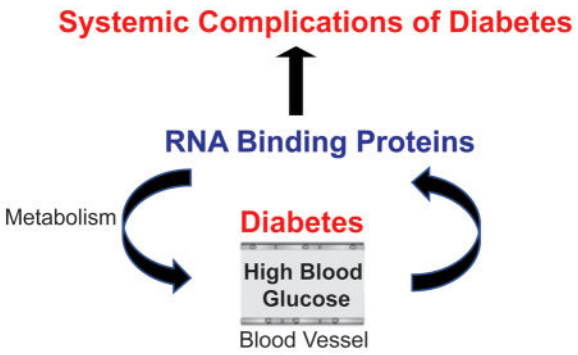

Keywords

RNA binding proteins; diabetes; therapy; RNA; post-transcriptional gene expression

Introduction

Diabetes

Diabetes is a group of metabolic disorders in which blood glucose levels are abnormally high. In Type 1 diabetes (T1D), blood glucose levels rise due to the destruction of pancreatic beta islet cells via autoimmunity that causes low or no insulin production (Fig. 1). In Type 2 diabetes (T2D), the insulin production is unable to stimulate glucose uptake into target tissues liver, adipose and skeletal muscle, increasing blood glucose levels (Fig. 1). Defects in insulin-mediated uptake of glucose into these target tissues cause chronic hyperglycemia in the bloodstream and triggers pathogenic signals including inflammation, hypertension, mitochondrial dysfunction, oxidative stress, endoplasmic reticulum (ER) stress, and dyslipidemia. Chronic hyperglycemia leads to systemic complications and increases the risk for cancer, infections and Alzheimer's disease [1, 2]. Systemic complications of diabetes include: a) vascular disease that can lead to heart attack and/or stroke [3, 4], b) neuropathy which causes pain and numbness [5–7], c) retinopathy that can progress into blindness [7–9], d) nephropathy, the biggest contributor to end-stage renal disease among diabetics [5–7], e) cardiomyopathy that can result in heart failure [10–12] and f) skeletal muscle myopathy that induces muscle wasting and weakness[13, 14] (Fig. 2).

Due to the multi-systemic manifestations, diabetes is a major health care problem, costing ~ $322 billion per year in the US alone. Recent advancements in RNA-based technologies indicate that RNA-regulatory networks controlled by RNA binding proteins (RBPs) are modulated in diabetes and contribute to systemic manifestations of diabetes. Therefore, we will discuss how changes in RBPs: LIN28, RBFOX2, FTO,IGF2BP2, eIF4E, CELF1 and HuR disrupt post-transcriptional RNA programs in diabetes and play a central role in development of diabetes and diabetic complications. We will also review how RBPs can be targeted using RNA-centric therapies to treat diabetic complications, based on the current progress made in such therapeutics.

RNA binding proteins

There is increasing evidence that many RBPs and RBP-regulated RNA networks are disrupted under diabetic conditions. RBPs are critical for post-transcriptional gene expression. They bind to RNA based on sequence and/or RNA structure and form ribonucleoprotein (RNP) complexes [17–20]. The interactions of RNA with different RBPs are highly dynamic and necessary for distinct steps of RNA biogenesis including 5′ capping, pre-mRNA splicing, 3′ mRNA cleavage and polyadenylation, mRNA export, mRNA editing and methylation, mRNA localization, mRNA decay and translation [17–20].

RBPs are important regulators of cell survival and function, because they have essential roles in fundamental cellular processes such as proliferation, differentiation, and apoptosis [17, 21, 22]. Dysregulation of RBPs has been observed in a plethora of diseases including cancer, (reviewed in [17, 22]), neurological (reviewed in [23, 24]), and cardiovascular diseases (reviewed in [25–28]). Several RBPs have been associated with the development of diabetes or with diabetic complications [29–36]. RBPs that are implicated in diabetes are summarized in Table 1. For example, Elav-like protein 1 (*Elavl1*) (HuR), hnRNP K, hnRNP F, YBX1, Insulin like growth factor 2 mRNA-binding protein 2 (IGF2BP2/IMP2), and LIN28 are dysregulated in diabetic kidneys and have been associated with diabetic nephropathy [37–44]. Quaking (QKI) [45, 46], tristetraprolin (TTP) [47, 48], ADAR1 [49], hnRNP C [50], HuR [51] and calreticulin (CALR) [52] are linked to atherosclerosis and/or vascular endothelial dysfunction. CUG triplet repeat binding protein ELAV-like family member 1 (CUGBP1/CELF1), RNA binding protein Fox-1 homolog 1 (Rbfox1), and eukaryotic initiation factor 4E (eIF4E) have been associated with diabetic skeletal muscle myopathy [53–56]. RNA binding protein Fox-1 homolog 2 (Rbfox2), CELF1, LIN28, HuR and QKI are implicated in diabetic cardiomyopathy [28, 57–62]. RBPs eIF4E and HuR are involved in diabetic retinopathy [63–68]. Polymorphisms in fat mass and obesity associated protein (FTO) are associated with obesity and kidney disease [33–36, 69].

In this review, we will only focus on seven of these RBPs: LIN28, Rbfox2, FTO, IG2BP2, CELF1 and HuR and the RNA regulatory processes they control (Table 1). We will start with the post-transcriptional mechanisms disrupted in diabetes, and follow up with RBPs that regulate these processes. Then, we will describe how these RBPs are dysregulated under diabetic conditions and their contribution to disease pathogenesis (Table 2). Finally, we will finish up by reviewing new therapies that target RBPs for treatment of human diseases and discuss their potential in the treatment of diabetic complications.

POST-TRANSCRIPTIONAL MECHANISMS ALTERED IN DIABETES

Alternative splicing (AS)

The alternative splicing regulators CELF1, Rbfox2, Rbfox1, QKI, and hnRNPC are implicated in diabetes by affecting alternative splicing decisions [28, 45, 46, 50, 53, 60–62]. Splicing is a process by which the non-coding regions (introns) of the pre-mRNA are removed and coding regions (exons) are joined together. Splicing occurs co-transcriptionally and is mediated by the spliceosome complex composed of ~100 auxiliary proteins and 5 small nuclear RNAs (snRNAs) (reviewed in [70, 71]). Although snRNAs catalyze the splicing

reactions, RBPs bind to the pre-mRNA and help define exons and splice recognition sites, thereby facilitating removal of introns [70].

AS can directly affect gene expression and increase protein diversity by allowing differential inclusion/exclusion of exons in some cases parts of introns, generating multiple protein isoforms from a single gene [70–72]. RBPs control AS decisions via binding to the pre-mRNA and communicating with the spliceosome components to promote or prevent exon inclusion [70]. Regulation of AS by RBPs is highly specific and precisely regulated especially during organism development and the cell cycle [73–77].

AS plays a crucial role in the development of T1D [78]. T1D is caused by autoimmune-mediated destruction of pancreatic beta-islet cells that produce insulin. AS impacts expression and function of the genes necessary for beta-islet cell function and auto-immunity [78–82]. In this review, we will focus on the role of AS defects in diabetic complications as the contribution of AS dysregulation to islet cell dysfunction and increased inflammation in T1D has been recently reviewed [78].

Genome wide AS changes are identified in both the diabetic heart and retina (Table 1) [83]. In diabetic retina, photoreceptor genes (*arrestin*, *Impg2*, and *Trpm1)* relevant to retina function are mis-spliced [83]. In diabetic hearts, genes with important roles in macromolecular metabolism, calcium ion homeostasis and cell cycle are aberrantly spliced [28]. We identified Rbfox2 as a major regulator of AS defects in diabetic hearts and a contributor to cardiac complications [28]. Role of Rbfox2 in diabetic complications will be discussed in detail in the next section. According to our findings, among 967 AS changes in diabetic hearts, a subset of genes displayed fetal/newborn splicing patterns. Further studies have shown that one of the hallmarks of diabetes-induced AS changes is the reactivation of fetal/newborn-like splicing patterns in adult diabetic hearts and skeletal muscle [53, 62]. Inappropriate expression of fetal/newborn spliced variants in adult tissues may contribute to muscle pathogenesis in diabetes.

One of the genes that is differentially spliced in diabetes is vascular endothelial growth factor (VEGF), a key component in vasculogenesis and angiogenesis and a central pathogenic factor in diabetes [8, 84, 85]. AS of *VEGF* exon 8 determines the pro- or anti-angiogenic properties of VEGF [85–89]. In the diabetic retina, *VEGF* switches to a pro-angiogenic spliced isoform and causes increased vascularization associated with retinopathy [89]. AS of *VEGF* exon 7 affects its function by regulating its solubility. In the kidneys of T2D patients, AS of *VEGF* generates more soluble VEGF, which is associated with worse parameters of diabetic nephropathy [87]. These studies suggest that mis-splicing of VEGF contribute to diabetic complications in the kidney and retina.

Another example of a mis-spliced gene relevant to diabetes pathogenesis is myocardin. Myocardin is a transcriptional co-activator vital for contractile gene expression in vascular smooth muscle cells (VSMCs) [46]. AS of *myocardin* is dysregulated in atherosclerosis, a common complication in diabetic patients [46]. VSMCs isolated from atherosclerotic patient plaques expressed *myocardin* spliced isoforms that cause increased proliferation and lower

contractility contributing to vascular pathology [46]. Together, these findings show that AS patterns affecting essential gene function are disrupted in diabetes.

RNA methylation

RNA methylation was discovered in the 1970s [90]. Discerning the functional consequences of this modification on RNA metabolism and gene expression are made possible by the recent technological advances in high throughput RNA sequencing combined with our ability to detect specific forms of methylated RNAs.

RNA methylation is a reversible modification that plays key roles in post-transcriptional gene regulation [91, 92]. It is analogous to DNA epigenetic modifications such that it can be written, read, and erased [91, 92]. The most abundant and highly conserved reversible mRNA modification in eukaryotes is N^6-methylation of adenosine (m^6A) [91, 92]. Genome wide m^6A RNA methylation analysis using m^6A-specific methylated RNA immunoprecipitation followed by next-generation RNA sequencing (MeRIP-Seq) allowed the discovery of methylation in both mRNAs and non-coding RNAs [93]. m^6A modification of RNA involves methyltransferases as writers such as METTL3, METTL14, and WTAP; demethylases as erasers including FTO and ALKBH5, and readers such as YTHDF proteins. Reader proteins bind to the methylated RNA and influence splicing, mRNA stability, localization and translation [91, 92]. Notably, RNA demethylase FTO polymorphisms are associated with obesity, which is a common feature of T2D [33–36]. In addition, m^6A methylation of mRNAs is decreased under diabetic conditions consistent with upregulation of FTO levels (Table 1) [94].

mRNA stability/degradation

mRNA stability is altered in diabetes via RBPs or microRNAs. In this review, we will address RBP-regulated mRNA decay in diabetes (Table 1). mRNA levels can be regulated post-transcriptionally via degradation as a quick mechanism to control gene expression in response to stimuli [95–97]. Removal of the 5′ cap structure by decapping enzymes induces mRNA degradation [96]. Similarly, removal of the 3′ poly(A) tail by deadenylases causes mRNA decay [96]. There are several cis-acting elements within the mRNA that signals for degradation. These elements can be present in the 5′ or 3′ untranslated regions (UTRs) as well as within the coding region of the mRNAs [98]. RBPs typically bind to these cis-acting elements within the mRNA to promote or prevent mRNA decay through interactions with decapping and/or deadenylation enzymes [95–97].

One of the well characterized cis-acting elements for regulation of mRNA stability are AU-rich elements (ARE) found in the 3′UTRs. mRNAs that contain ARE elements are rapidly degraded. RBPs such as HuR and TTP bind to AREs and control the degradation of ARE-containing mRNAs [98]. Under diabetic conditions, mRNA levels of ARE-containing mRNAs such as *NOD2*, *CTGF*, *TGFB1*, *SNAI1*, *TNF*, *FOS*, *EGR1*, *p21*, and *FOS* are elevated due to changes in subcellular localization, protein levels and activities of ARE-binding proteins HuR and TTP [39, 40, 47, 48]. HuR binding to the ARE elements stabilizes mRNAs [98]. Increased levels of HuR in the cytoplasm is thought to contribute to the increase in levels of these ARE containing mRNAs genes. Another gene that is upregulated in obese mouse

hearts via increased mRNA stability is *FoxO1* [60]. *FoxO1* is an important regulator of insulin signaling and contributor to ER stress in diabetic hearts. mRNA levels of *FoxO1* are increased under diabetic conditions via QKI mediated changes in its mRNA stability. QKI is shown to promote *FoxO1* mRNA degradation and changes in QKI in diabetic hearts are thought to cause increased levels of FoxO1. mRNA levels of *glucose transporter-1* (*GLUT1*), which is necessary for glucose uptake by the cells, are altered in VSMCs under high glucose conditions [52]. QKI is shown to control GLUT*1* mRNA decay [52]. Altogether, these studies suggest that mRNA stability is affected in diabetes via different RBPs. The role of HuR in mRNA stability and diabetes pathogenesis will be discussed in detail in the next section.

mRNA translation

Regulation of mRNA translation occurs mostly at the rate limiting initiation step [99–104]. To start protein synthesis, the cap-binding protein eIF4E, binds the cap structure at the 5′ end of the mRNAs and helps recruit the small ribosomal subunit via interaction with other translation initiation factors eIF4G and eIF3 [102, 104]. Then, the large ribosomal subunit is recruited to the 5′ end of the mRNA with help from other translation initiation factors to start cap-dependent translation [102, 104]. Alternatively, some eukaryotic mRNAs utilize internal ribosome entry sites (IRES) to load ribosomes onto the mRNA independent of 5′ cap and translate in a cap-independent manner [102, 105].

Under diabetic conditions, cap-dependent translation is inhibited at the initiation step due to low cap binding activity of eIF4E (Table 1). 4E-binding protein (4E-BP1) binds to eIF4E and blocks eIF4E interaction with the 5′ cap of mRNAs under diabetic conditions [54–56, 66–68, 106–111]. Regulation of eIF4E by 4E-BP1 is affected under diabetic conditions and will be further discussed in the next section.

While cap-dependent translation is inhibited in diabetes, IRES-dependent translation of stress induced mRNAs is stimulated [112, 113]. Since diabetic conditions affect mRNA translation preferentially favoring IRES dependent translation, future studies using ribosomal profiling followed by RNA-sequencing, are necessary to identify mRNAs that are actively being translated under diabetic conditions.

RNA BINDING PROTEINS IMPLICATED IN DIABETES

Diabetes are a group of metabolic disorders in which insulin signaling, glucose and fat metabolism are altered. Abnormal metabolism in diabetes activates pathogenic events such as inflammation, ER stress, oxidative stress, fibrosis and epithelial-mesenchymal transition (EMT) of cells. Figure 3 summarizes specific RBPs that contribute to some of the pathogenic events triggered in diabetes. In this part, we will discuss **a)** the roles of these specific RBPs: LIN28, Rbfox2, CELF1, FTO, eIF4E, and IGFBP2 in RNA metabolism, **b)** dysregulation of these RBPs in diabetes, and **c)** contribution of these RBPs to development of diabetes and diabetic complications.

LIN28

LIN28A/B is an RBP involved in microRNA biogenesis, RNA splicing, and mRNA translation [114–116]. LIN28 binds looped RNA structures in pre-let7 RNA and blocks production of mature let7 microRNA, thereby affecting expression of let7 target genes. It has been shown that LIN28 can also bind to other RNAs with structural similarity to pre-let7 RNA that exhibit GGAG sequences [117].

LIN28 is important for embryonic development, pluripotency of stem cells, growth, and metabolism [114, 118, 119]. LIN28 has a role in AS via interacting with hnRNPA1 [115]. In addition, LIN28 modulates AS by controlling mRNA translation of the splicing regulators hnRNPF, TIA-1, FUS/TLS and TDP-43 [117]. A new study shows that LIN28 binds to specific gene promoters and may regulate transcription [120].

Relevant to diabetes, LIN28 has a critical role in controlling glucose metabolism, mitochondrial function and insulin resistance [119, 121–123]. More specifically, LIN28 increases glucose uptake by cells and prevents insulin resistance in high fat induced diabetic mice. This is mediated in part by its role in processing and maturation of let7 miRNA [123]. On the other hand, muscle specific deletion of LIN28 increases insulin resistance independent of effects on let7 microRNA; indicating that other functions of LIN28 in RNA metabolism are important for insulin sensitivity. LIN28 is strongly linked to insulin resistance and T2D [38, 57, 58, 119, 121, 123]. LIN28 regulates mRNA translation of HMGA genes [124], which are also genetically associated with insulin resistance and T2D [125]. LIN28 regulates translation of mRNAs that are involved in oxidative phosphorylation [122]. In addition, LIN28 helps control glycolysis in kidney cells [126] and in cancer cells and hepatocellular carcinoma [127].

LIN28 is implicated in kidney and cardiac complications of diabetes [38] (Table 2). *LIN28* mRNA levels are increased in T1D and T2D mouse kidneys via transcriptional activation by SMAD2/3 (Table 1) [38]. Upregulation of LIN28 leads to changes in Let7b target genes, which include *Col1a2* and *Col4a1* contributing to kidney fibrosis in T1D and T2D mouse kidneys [38]. Conversely, LIN28 levels are decreased in T1D mouse hearts (Table 1) [57, 58]. Low LIN28 levels correlate with cardiomyocyte apoptosis and decreased contractile function [58]. In support of its role in diabetic hearts, LIN28 overexpression alleviates mitochondrial dysfunction and cardiomyocyte apoptosis preventing cardiomyopathy in T1D mice [58]. LIN28 depletion exacerbates cardiac symptoms in diabetic mice [57, 58]. These studies support a critical role for LIN28 in diabetic heart and kidney disease.

RNA binding protein Fox-1 homolog 2 (Rbfox2)

Rbfox2 is implicated in cardiac complications of diabetes. Rbfox2 belongs to a family of RBPs that include Rbfox1 and Rbfox3. Rbfox proteins bind the (U)GCAUG motif in RNA and regulate AS [128–134]. While Rbfox1 and Rbfox2 are widely expressed in different tissues, Rbfox3 is neuron specific. Rbfox1 and Rbfox2 control motor neuron function and development of the brain cerebellum [135] as well as skeletal muscle and heart function [128, 130, 136, 137].

Rbfox2 has essential roles in AS regulation in the brain, skeletal muscle, heart and embryonic stem cells [130, 132, 135–137]. In skeletal muscle, Rbfox2 controls fusion of myoblasts during skeletal muscle differentiation [128]. In the heart, conditional deletion of Rbfox2 in mouse cardiomyocytes leads to dilated cardiomyopathy [130]. In addition, Rbfox2 protein levels are downregulated in hearts undergoing pressure overload induced heart failure [130]. Consistent with its important role in the brain and the heart, Rbfox2 mutations have been identified in patients with congenital neurodevelopmental and cardiac defects [138]. Importantly, Rbfox2 contributes to genome wide gene expression changes observed in patients with congenital heart defects [27].

Recent studies defined new functions for Rbfox2 in regulating transcription via interactions with the polycomb complex [129] and in microRNA processing [139]. Due to its importance, genome-wide RNA targets of Rbfox2 have been identified using CLIP-sequencing in several different cell types [128–134]. Rbfox2 is a master regulator of post-transcriptional gene expression as it controls expression levels of other RBPs via AS-dependent nonsense-mediated mRNA decay [132–134].

Rbfox2 protein levels are upregulated in T2D human patient hearts and T1D mouse hearts, correlating with PKCα/βII activation in the diabetic heart (Tables 1 and 2) [28, 62, 140–142]. Though Rbfox2 protein levels are elevated in the diabetic heart, Rbfox2 splicing function is adversely affected [28] due to increased expression of a spliced isoform with dominant negative activity [28, 143, 144]. In T1D mouse hearts, Rbfox2 is a major contributor to genome-wide AS changes [28, 62]. 69% of transcripts mis-spliced in diabetic hearts display Rbfox2 binding sites within alternative exons and/or flanking introns [28.] Dysregulation of Rbfox2 impairs proper expression of cytoskeleton-associated genes and intracellular calcium handling in primary cardiomyocytes [28]. These results indicate that dysregulation of Rbfox2 contributes to the cardiac complications of diabetes (Table 2).

A recent study has found that Rbfox2 is vital for insulin secretion and survival of beta islet cells in the pancreas [82]. AS function of Rbfox2 is linked to EMT [145, 146], which is one of the pathogenic events that contribute to diabetic nephropathy, retinopathy and atherosclerosis. More studies are needed to determine whether Rbfox2 contributes to these diabetic complications.

Fat mass and obesity-associated protein (FTO)

FTO is an m^6A specific demethylase that removes methyl groups in RNA which in turn controls the fate of the RNA in the cell [91, 92]. FTO is implicated in DNA repair and cell survival [147]. Genetic and molecular studies strongly associate FTO to obesity and adipogenesis [148] through FTO's ability to regulate energy production by mitochondria [149] and its role in differentiation of fat cells [148].

In T2D patients and diabetic rats, FTO levels are elevated with a corresponding decrease in genome wide m^6A modification of mRNAs [94] (Tables 1 and 2). Polymorphisms in FTO are associated with obesity in humans [33–36]. FTO mutations are also linked to renal fibrosis in humans with chronic kidney disease [69]. Therefore, FTO association to obesity may predispose individuals to T2D. Recent studies indicate that FTO may play a role in

neurogenesis [150] and myogenesis [149], both of which are also affected in diabetes. Further studies are needed to characterize the contribution of FTO to diabetic complications including neuropathy, nephropathy and myopathy (Table 2).

Insulin like growth factor 2 mRNA-binding protein 2 (IGF2BP2/IMP2)

IGF2BP2 is an important regulator of insulin signalling. It binds target mRNAs and controls their localization, stability and translation. One of the well-known targets of IGF2BP2 is the insulin-like growth factor (IGF). IGF2BP2 binds to IGF mRNA and controls its translation mediated by an IRES element [151]. Some other translationally-regulated targets include *c-myc, SP1* and *Igf1r* [152]. Importantly, IGF2BP2 is identified as a strong susceptibility gene for T2D in many human genetic studies [29–32]. IGF2BP2 is also critical for skeletal muscle stem cell activation and proliferation [152], which are disturbed in diabetic skeletal muscle. In addition, IGF2BP2 levels are downregulated under diabetic conditions due to changes in its transcription mediated by transcription factor HMGA2, which is a risk allele for T2D (Table 1).

IGF2BP2 is an important factor in pathogenesis of diabetic nephropathy (Table 2). It binds to *Laminin-β2* (*LAMB2*) mRNA and regulates its localization to the actin cytoskeleton and activates its translation [37]. LAMB2 protein is important for proper kidney function and preventing proteinuria. In T1D rat kidneys, IGF2BP2 protein levels are reduced correlating with low LAMB2 protein levels [37]. In sum, IGF2BP2 likely contributes to the development of diabetes due to its role in insulin signaling and to diabetic kidney manifestations (Table 2).

Eukaryotic initiation factor 4E (eIF4E)

eIF4E is a translation initiation factor that binds to the 5′cap structure and initiate translation via recruiting the ribosomal subunits to the 5′ end of eukaryotic mRNAs [102]. eIF4E is necessary for cell survival and organism development [153, 154]. As a downstream effector of the mTOR signaling pathway, eIF4E is implicated in diabetes. Recently, it has been found that the commonly used diabetes drug named metmorfin not only affects AMPK but also mTOR and ERK pathways and influences eIF4E dependent mRNA translation [155, 156].

eIF4E activity is controlled via phosphorylation by MAPK-activated protein kinase (Mnk) that increases its cap-binding activity [157]. eIF4E cap binding activity is also tightly regulated via 4E-BP proteins, which bind eIF4E and inhibit its binding to the 5′ cap [102, 107]. 4E-BP proteins are important regulators of eIF4E (Table 1). High glucose levels affect the 4E-BP proteins that blocks eIF4E binding to the cap leading to inhibition of cap dependent mRNA translation [111]. It has been found that the mTOR/4E-BP1/eIF4E pathway is a regulatory network for proper cardiomyocyte function and survival [154] and for mitochondrial biogenesis [153].

In diabetes, 4E-BP1 is modulated by several different mechanisms. Many studies show that 4E-BP1 protein levels are increased under diabetic conditions [66, 67, 110]. This increase in 4E-BP1 causes binding to eIF4E blocking its interaction with the 5′ cap of mRNAs. 4E-BP1 is also phosphorylated by mTOR leading to the release of eIF4E from 4E-BP1 [157]. In diabetes, decreased phosphorylation of 4E-BP1 by mTOR reduces eIF4E cap binding activity. 4E-

BP1 also undergoes O-GlcNAcylation where *N*-Acetylglucosamine is added to Ser or Thr residues of 4E-BP1 [66, 67, 110]. Increased O-GlcNAcylation of 4E-BP1 under diabetic conditions strengthens binding to eIF4E, inhibiting cap dependent translation [66, 67, 110].

eIF4E/4E-BP is also important in the development of insulin resistance. Increased activation of 4E-BP1 protects against diet-and age-dependent insulin resistance [158]. Furthermore, 4E-BP2 contributes to pancreatic beta cell loss in T1D [159]. In the diabetic retina, eIF4E cap binding activity is repressed due to increased 4E-BP1 levels contributing to diabetic retinopathy [66, 68] (Table 2). This leads to a decrease in cap-dependent protein synthesis while IRES mediated translation of *VEGF* mRNA is stimulated [66–68, 110]. Deletion of 4E-BP1 in the rodent retina inhibits hyperglycemia induced upregulation of VEGF [66] and delays diabetes induced blindness [67].

In T1D rat hearts and skeletal muscle, protein synthesis is decreased mostly due to low eIF4E activity [54–56] and this is thought to contribute to skeletal muscle myopathy and cardiomyopathy (Table 2). Notably, insulin treatment ameliorates eIF4E-dependent translation inhibition under diabetic conditions [54–56]. Even though changes in eIF4E can block global translation, phosphorylation of eIF4E via TGFB1 signalling promotes translation of specific genes that promote EMT [160] contributing to diabetes pathogenesis.

It has been previously established that translation regulation is closely linked to metabolic dysfunction and diabetes. For instance, mutations in the eukaryotic translation initiation factor 2α kinase 3 that regulates translation initiation factor eIF2, cause Wolcott-Rallison syndrome. This genetic disorder is characterized by neonatal onset of diabetes [161]. These genetic associations as well as molecular perturbations in translation factors and regulators of translation factors provide a strong link between translation regulation and diabetes.

CUG triplet repeat binding protein ELAV-like family member 1 (CUGBP1/CELF1)

CELF1 was identified as an RBP that binds to CUG triplet repeat RNA [162]. Further studies showed that it could bind to GU- and UG-rich sequences [163–165]. Genome wide RNA targets of CELF1 and its consensus binding sites were identified using CLIP-seq and Bind-n-seq [166, 167]. CELF1 is a multi-functional RBP that has established roles in AS, mRNA stability and translation [164, 168–172]. Its role in translation, mRNA stability and AS regulation have been implicated in the pathogenesis of Myotonic Dystrophy [171, 173–177]. Conditional overexpression of CELF1 in mouse skeletal muscle causes skeletal muscle wasting reproducing several aspects of Myotonic Dystrophy muscle pathology [174]. Ablation of CELF1 in mice affects growth, viability, and fertility [178]. CELF1 also has an important role in the maturation of the heart after birth [179].

CELF1 has vital roles in glucose and energy metabolism. CELF1 regulates splicing of insulin receptor. Increased expression of CELF1 induces a splicing change in the insulin receptor that leads to expression of an isoform with lower signalling potential thereby contributing to insulin resistance in Myotonic Dystrophy [180, 181]. Furthermore, CELF1 controls splicing of pyruvate kinase, which is necessary for glycolysis [182]. Increased expression of CELF1 in pre-adipocytes impairs adipogenesis in a TNF-alpha dependent manner [183]. CELF1 also controls mRNA translation of genes that promote EMT [163]. CELF1

protein levels are regulated by PKC- and ERK-mediated phosphorylation [184, 185]. Related to diabetes, CELF1 protein levels are elevated in T1D mouse skeletal and heart muscle (Tables 1 and 2) [53]. Consistent with activation of ERK and PKC under diabetic conditions, protein levels of CELF1 are upregulated in the diabetic skeletal muscle and heart; correlating with abnormal AS patterns of its targets (Tables 1 and 2). [53, 62]. Importantly, increased CELF1 levels in diabetes may impair glucose metabolism and insulin receptor signalling through regulation of AS of essential genes with roles in metabolism.

CELF1 overexpressing mice develop dilated cardiomyopathy and heart failure and display reactivation of embryonic splicing patterns [175]. These phenotypic and molecular changes in CELF1 transgenic mice are similar to the changes observed in the diabetic skeletal muscle and heart. We have found that CELF1 protein levels are elevated in diabetic skeletal muscle and heart consistent with increased expression of fetal/newborn spliced isoforms of CELF1 targets [53, 62]. Thus, increased CELF1 protein levels in diabetic heart and skeletal muscle might be an important factor in skeletal muscle weakness and atrophy and diabetic cardiomyopathy (Table 2). However, more studies are needed to further investigate this possibility.

Elav-like protein 1 (*Elavl1*) (HuR)

HuR is a multi-functional RBP implicated in many aspects of diabetes pathogenesis. It binds to polyU and AU-rich elements and regulates mRNA stability and translation [186–188]. HuR shuttles between the nucleus and cytoplasm [189] and upon activation, translocates to the cytoplasm and controls target mRNA stability and translation [189]. Phosphorylation by PKC controls mRNA binding activity and cytoplasmic localization of HuR [190].

HuR is a key regulator of genes involved in stress response, cell cycle, inflammation, and immune response [98, 191]. Deletion of HuR in mice causes loss of hematopoietic stem cells and early postnatal death [192]. HuR is implicated in apoptosis via controlling mRNA levels of the p53 regulator mdm2 [192]. Depletion of HuR impairs the inflammatory response in human umbilical cord endothelial cells in a interleukin 10 dependent manner [193, 194] and contributes to TNF-α mediated cell death and inflammation in primary human cardiomyocytes [59]. As a regulator of mRNA decay, HuR affects the stability of m^6A containing mRNAs and impacts pluripotency of embryonic stem cells [195]. It binds and stabilizes *Sirt1* mRNA [196], VEGF and TNF-alpha mRNAs [188]. HuR also has roles in AS and polyadenylation [188, 189, 197]. Its role in RNA splicing is linked to angiogenesis and mitochondrial function [198].

It has been shown by many groups that HuR levels are increased in diabetes via different mechanisms (Table 1) [40, 59, 65]. First mechanism is the phosphorylation of HuR by PKC that leads to high HuR protein levels, and increased cytoplasmic localization of HuR in cells under diabetic conditions [51, 65]. Second mechanism for HuR increase in diabetes is through micro-RNA mediated regulation. Although HuR is also controlled via many microRNAs, under diabetic conditions two specific microRNAs are identified as regulators of HuR [59]. MiR-23 and miR9, which control HuR levels, are downregulated under diabetic conditions [59,199]. Low levels of miR23 and miR9 lead to increased HuR protein levels in diabetic tissues.

HuR is a major contributor to diabetic manifestations including retinopathy and nephropathy (Table 2). Depletion of HuR improves retinal damage in diabetic mice [63]. In diabetic patient kidneys, HuR is upregulated in the cytoplasm [40]. The increase in HuR stabilized the mRNA levels of *CTGF*, *TGFB1*, *FOS*, and *SNAIL*, contributing to EMT and diabetic nephropathy [39]. Silencing of HuR in T1D rats partly ameliorated kidney proteinuria, inflammation, and hypertrophy [40]. Together these studies strongly support the hypothesis that HuR up-regulation contributes to the development of diabetic nephropathy and retinopathy. Upregulation of HuR in diabetic human hearts correlated with increased inflammatory markers that can lead to cardiomyocyte death [59]. Silencing of HuR in mice reduces infarct size after myocardial infarction [193]. These results suggest HuR may be a common mediator of diabetic complications in multiple tissues; and as such, a good target for systemic treatment options because it binds specific RNA sequences.

In summary, changes in these seven RBPs contribute to pathogenic events activated under diabetic conditions such as inflammation, EMT, mitochondrial dysfunction and fibrosis in diabetes (Fig. 3). Importantly, a majority of these RBPs have key roles in insulin signaling, and metabolism of fat and glucose, which influence the development of diabetes.

RNA-BASED THERAPEUTICS IN DIABETES

RBPs play a critical role in the development of T1D and T2D diabetes as well as in diabetic complications. Targeting the interaction between RBPs and their RNA targets could be an effective strategy to correct gene expression changes in diabetic patients. RNA-based therapies show promise in the treatment of several human diseases detailed below.

Many different RNA-based technologies have been used for therapeutic purposes. We will focus on anti-sense oligo (ASO) based therapy, which is successfully being used in clinics. ASOs are single-stranded deoxyribonucleotides that are usually modified, including the addition of methyl or fluoro groups for increased stability and uptake [200, 201]. ASOs are highly flexible in that they can be designed to degrade or stabilize target RNA, inhibit or enhance translation of target RNAs, modulate splicing of a pre-mRNA, or modify RBP binding to RNA [201]. Importantly, ASOs have reported mild side effects with almost no immune response, thus they are generally considered safe for the treatment of human diseases [202, 203].

An ASO based drug that blocks RBP binding to RNA is now used for the successful treatment of spinal muscular dystrophy (SMA). The *SMN1* gene is mutated in patients with SMA and is the cause of progressive loss of motor neurons [204, 205]. *SMN1* mutations reduce SMN1 protein levels resulting in impaired motor neuron function. Therefore, children with this mutation suffer from severe muscular atrophy and weakness, which can lead to death [206]. Recent clinical trials that used an ASO to restore *SMN* gene function improved motor function in patients with infantile-onset and late-onset SMA [207, 208].

SMA-specific ASO targets *SMN2* gene, which is closely related to *SMN1* but is normally degraded due to the exclusion of exon 7. SMN2 spliced isoforms including exon 7 can partially replace SMN1 protein function [209, 210]. The ASO promotes *SMN2* exon 7 inclusion

by blocking the RBP hnRNP-A1/A2 binding site to the RNA, thereby generating more full-length SMN2 protein [209]. Since ASOs work well in modulating splicing [211, 212], diabetes-induced AS changes may be corrected by modulating RBP binding to target RNAs using specific ASOs.

Modulation of eIF4E- and IRES-dependent translation by ASOs is actively being explored for cancer and HIV treatment (ClinicalTrials.gov). These translation-modulating ASOs could have important ramifications in diabetes since down-regulation of eIF4E-dependent translation [66–68, 106, 107] with an increase in IRES dependent translation [66, 68] is a common complication in diabetes. The clinical success of RNA-based therapeutics is encouraging for future applications as novel and effective therapy options for diabetic complications.

There are two completed clinical trials that used ASOs to improve insulin sensitivity and decrease dyslipidemia in diabetes patients [213, 214]. One of the ASOs designed to degrade hepatic glucagon receptor (GCGR) mRNA significantly attenuated hepatic glucose production [213]. Another ASO that targets degradation of apolipoprotein C-III mRNA resulted in lower plasma triglyceride levels and insulin resistance in T2D patients. Since RBP regulated RNA networks are disrupted in diabetes and contribute to diabetic complications, modulating RBP:RNA interactions in diabetic complications could be a promising therapy.

Some questions still remain about the tissue specificity of ASO treatments, but advances in tissue specific delivery are currently being investigated. The use of nanoparticles, exosomes, or direct injection to the muscle or lumbar region of the spine have proven efficacy for some tissue specificity [215, 216]. In addition, targeted uptake of ASOs by the liver using specific lipid conjugates has been successful [217]. Altogether, there are numerous opportunities in the diabetes field for RNA-centric therapies to improve patient health and lifespan.

Conclusion

Recent studies demonstrate that RBPs play key roles in the development of diabetes and its systemic manifestations. The technological advancements in identification of global RNA targets of RBPs in a wide variety of tissues will help determine the major RNA regulatory programs disrupted under diabetic conditions. Many studies reviewed here indicate that modulating RBPs in rodent models of diabetes can improve or even prevent symptoms of diabetes. In the future, RBP function can be modulated for treatment of a variety of diabetic complications using modified oligonucleotides or ASOs that can control RBP interactions with RNA. However, caution is necessary for drug design targeting RBPs as the same RBP can have differing or even opposite roles in different tissues. In summary, post-transcriptional regulation by RBPs is emerging as a key mechanism in the development and pathogenesis of diabetes and has the potential to provide new therapeutic options for diabetic patients.

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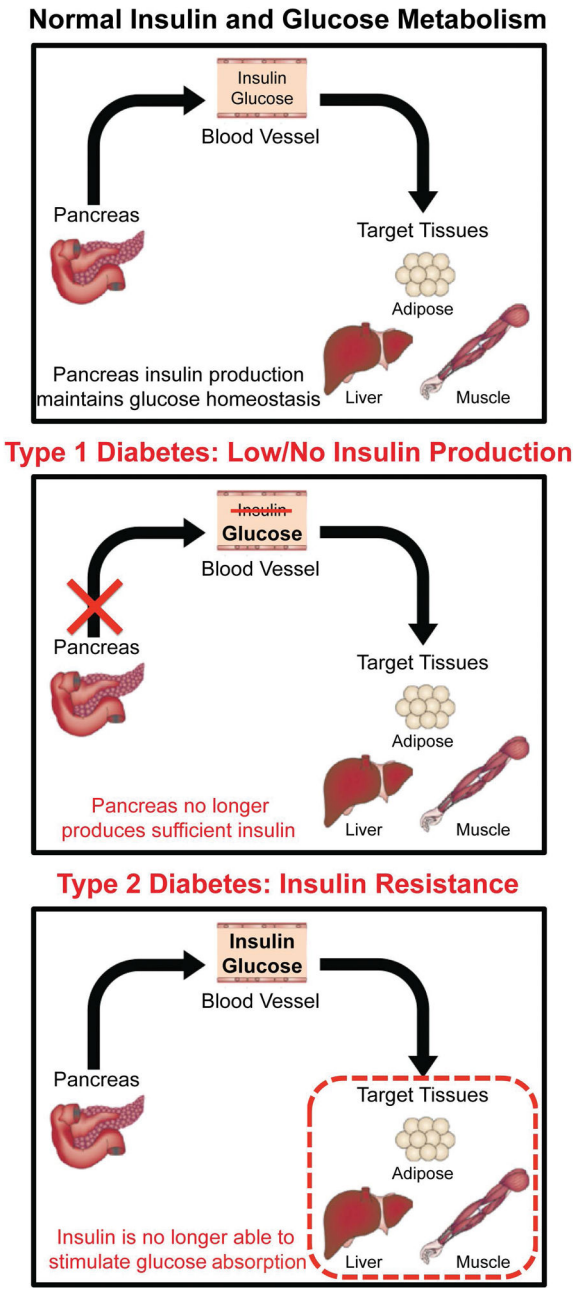

Figure 1. Glucose homeostasis in Type 1 and Type 2 diabetes

Pancreatic beta-islet cells secrete insulin to control glucose levels in the blood. Insulin allows glucose absorption into target tissues that include skeletal muscle, adipose tissue and liver to maintain normal glucose levels in the blood. In Type 1 diabetes, blood glucose levels increase because insulin is production is reduced due to the destruction of beta-islet cells in the pancreas. In Type 2 diabetes, insulin resistance prevents the efficient uptake of glucose into target tissues causing hyperglycemia.

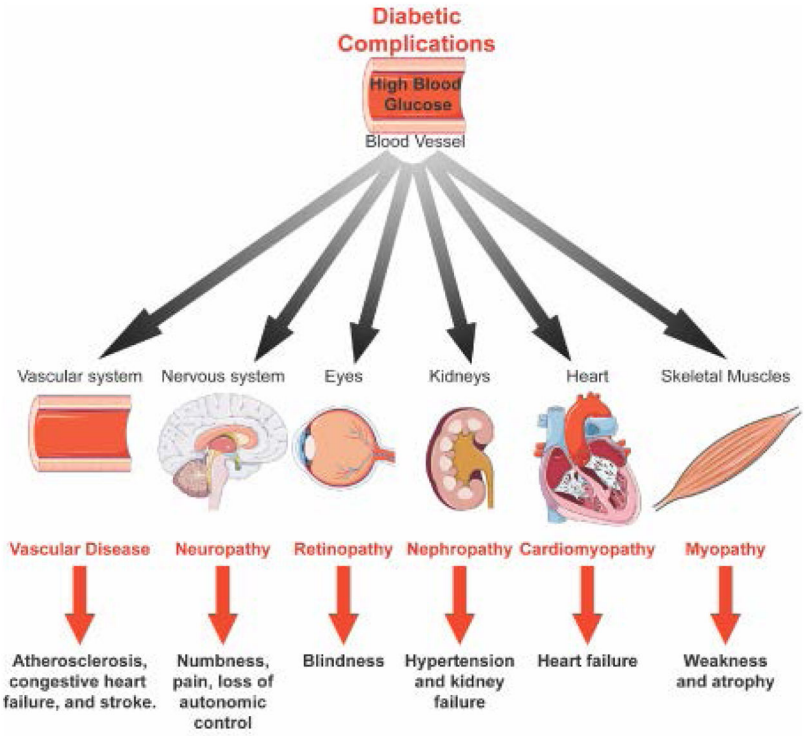

Figure 2. Systemic complications of diabetes

Diabetes increases the risk for coronary artery disease, which can block blood flow and cause heart attack and/or stroke [3, 4]. Hyperglycemia damages nerve fibers causing neuropathies that can adversely affect the digestive tract, urinary tract, heart and blood vessels [5–7]. Retinopathy is the leading cause of blindness in diabetic adults [7–9]. Almost half of diabetic patients develop diabetic nephropathy [5–7]. In most cases, patients develop kidney failure requiring dialysis [6]. Under diabetic conditions, heart muscle structure and function are impaired leading to cardiomyopathy [15, 16]. Diabetes also impacts skeletal muscle function causing muscle weakness and atrophy [13, 14].

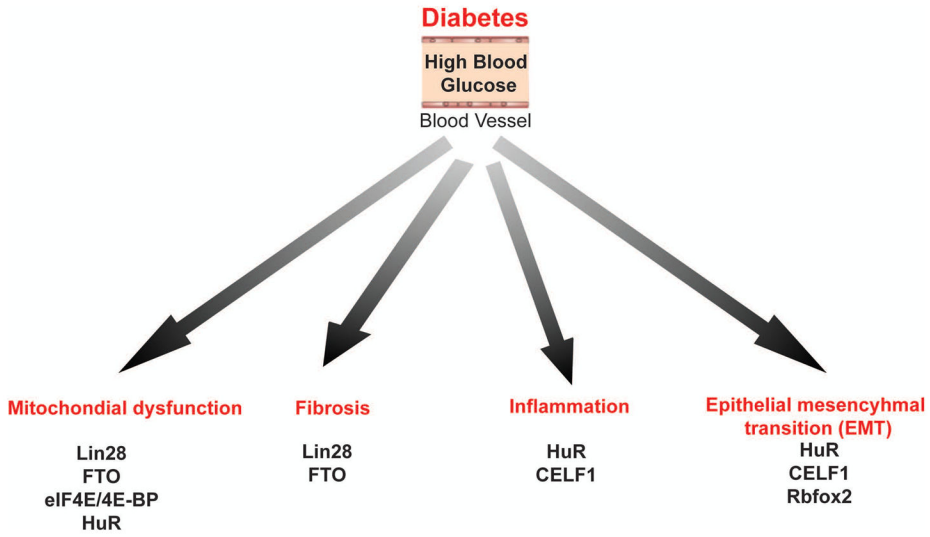

Figure 3. RNA binding proteins involved in pathogenic events triggered in diabetes

Chronic hyperglycemia initiates pathogenic signals that can cause mitochondrial dysfunction, fibrosis, inflammation and epithelial mesenchymal transition (EMT). RNA binding proteins that are implicated in diabetes associated pathogenic events are summarized.

Table 1

RNA binding proteins-post-transcriptional networks affected in diabetes and mechanism of diabetes induced changes in RNA binding proteins.

Post-transcriptional mechanisms affected in diabetes	**RBPs altered in diabetes**	**Diabetes induced changes in RBPs**	**Mechanism(s) that affect RBPs in diabetes**
mRNA translation microRNA biogenesis	LIN28	**Increased mRNA and protein levels** (diabetic kidney) **Decreased mRNA and protein levels** (diabetic heart)	Mediated by increased TGFB signaling and SMAD2/3 transcriptional activation (diabetic kidney) Unknown mechanisms (diabetic heart)
Alternative splicing	RBFOX2	**Increased protein levels** **Low splicing activity**	Mediated likely by PKCα/βII phosphorylation Mediated by increased expression of a dominant negative isoform
RNA methylation	FTO	**Increased mRNA levels**	Unknown mechanisms
mRNA translation mRNA localization	IGF2BP2	**Decreased mRNA and protein levels**	Transcriptional downregulation by HMGA2
mRNA translation	eIF4E	**Decreased activity**	Increase in protein levels and binding activity of 4E-BP1 that inhibits eIF4E mediated by increased O-GlcNAcylation and/or decreased phosphorylation
Alternative splicing	CELF1	**Increased protein levels**	Mediated by PKCα/βII phosphorylation
Alternative splicing mRNA decay mRNA translation	HuR	**Increased mRNA and protein levels** (diabetic heart) **Increased protein levels and localization to the cytoplasm** (diabetic retina, kidney)	Mediated by decreased miR-9 (diabetic heart) and miR23 Mediated by PKCβ phosphorylation (diabetic retina)

Table 2

Contribution of RNA binding proteins to diabetes pathogenesis.

RBPs	RBP target RNA(s) affected in diabetes	Diabetic complication(s)	Experimental Model(s)
LIN28A	**Let7 microRNA family**	**Diabetic nephropathy and cardiac complications**	**Db/Db T2D mouse kidney and STZ T1D mouse kidney and heart**
RBFOX2	***FXR1*, *MEF2A*, global alternatively spliced transcripts**	**Diabetic cardiac complications**	**STZ T1D mouse and human T2D patient heart**
FTO	**Global changes in A^6 methylated transcripts**	**Unknown**	**Human T2D patient and STZ T1D rat peripheral blood**
IGF2BP2	***LAMB2***	**Diabetic nephropathy**	**STZ T1D mouse kidney**
eIF4E	***VEGF* and genome wide transcripts**	**Diabetic myopathy, retinopathy, and cardiac complications**	**Alloxan induced T1D rat skeletal muscle and heart, STZ T1D rat retina, STZ T1D mouse and Akita T1D mouse liver and retina**
CELF1	**Global alternatively spliced transcripts**	**Diabetic myopathy and cardiac complications**	**NOD T1D mouse skeletal muscle and STZ T1D mouse heart**
HuR	***VEGF*, *CTGF*, *TGFB1*, *SNAI1*, *FOS*, and *NOD2***	**Vascular disease, diabetic nephropathy, retinopathy, and cardiac complications**	**Human diabetic patient heart and kidney biopsies, human T2D patient kidney biopsies, human patient vascular tissue, and STZ T1D rat kidney and retina**