Promiscuous molecules in specific tissues in order to achieve better therapeutic outcomes.

**miRNAs in Diabetes Complications**

There is a wealth of evidence on the diverse role of miRNAs in many biological processes, including proliferation, differentiation, apoptosis, and development. The list of diseases in which dysregulation of miRNAs has been implicated is constantly growing. Compared with cancer, far less is known about the role of miRNAs in diabetes and its complications. Several miRNAs have been identified as having a physiological role in tissues in which diabetes complications occur. Whether these miRNAs are involved in the damage that occurs in diabetes is yet to be established. The association between altered miRNA expression and the development and progression of the various diabetes complications implicates certain miRNAs in the development of diabetes-related injury in the heart, kidney, peripheral nerves, and retina. Given that each miRNA has the potential to regulate multiple genes, dysregulation of miRNAs would be certain to have impact on many biological processes that are of direct relevance to diabetes complications. As tempting as it is to have a blinkered approach to our favorite miRNA and target gene, it is naive to ignore the incredible complexity of miRNA regulation and the depth of the downstream maze of targets, both direct and indirect. This complexity is highlighted later in this article, demonstrating how both increased and decreased expression of certain miRNAs are associated with diabetes complications. A summary of the miRNAs relevant to diabetes complications is found in Table 1.

**Can We Identify Patients at Risk for Developing Complications?**

Gene profiling technology has been used with a view to improve disease diagnosis and prognosis, especially in the area of cancer research. Over a third of diabetes patients develop serious complications. Can we use miRNA profiling to identify patients that go on to develop complications?

One study observed increased expression of several miRNAs in the diabetic GK rat model, including increased expression of the miR-29 family in muscle, fat, and liver, correlating with insulin resistance (7). Another study profiled miRNA expression in skeletal muscle of the spontaneous diabetic GK rat and observed the downregulation of seven and overexpression of two miRNAs, with miR-24 showing the highest fold change (8). Kloting et al. (9) examined miRNA expression profiles in omental and subcutaneous fat deposits in control subjects and newly diagnosed diabetic patients. Interestingly, similar expression patterns were observed in both fat deposits for each patient, but differences were observed between patients based on parameters of obesity and metabolism. Zampetaki et al. (10) profiled miRNAs in the plasma of 800 patients in a prospective study of type 2 diabetic patients and established a diabetes signature based on ten miRNAs.
The kidney are myofibroblasts, arising from renal tubular cells via epithelial to mesenchymal transition (EMT) and endothelial cells via endo-MT, bone marrow derived cells and resident interstitial fibroblasts (12). Blockade of specific steps of EMT dramatically reduces fibrotic lesions in models of kidney fibrosis, including diabetes, highlighting the role of some aspects of the EMT pathway in nephropathy (12).

Recent attention has turned to the role of miRNAs in renal disease where Dicer knockout experiments have established the general importance of miRNA in normal renal development and function (13). Other studies have provided evidence linking prosclerotic factors and miRNAs to fibrosis (14–19) and have provided the much needed impetus in this area with the promise of new approaches for the treatment of fibrosis. Figure 1 shows the main miRNAs that have been reported to play a role in diabetic nephropathy and are outlined below.

**miR-192.** The role of miR-192 remains controversial and highlights the complex nature of miRNA research. Kato et al. (16) observed increased renal expression of miR-192 in streptozotocin (STZ)-induced diabetes and in the db/db mouse and demonstrated that transforming growth factor (TGF-β1) upregulated miR-192 in mesangial cells (MCs). miR-192 repressed the translation of ZEB2, a transcriptional repressor that binds to the E-box in the collagen 1a2 (col1a2) gene (16). They proposed that miR-192 repressed ZEB2 and resulted in increased col1a2 expression in vitro and contributed to increased collagen deposition in vivo. These data suggest a role for miR-192 in the development of the matrix accumulation observed in DN. Interestingly, miR-192 and a number of other miRNAs have also been correlated with disease severity and progression in patients with IgA nephropathy (20) and hypertensive nephropathy (21), suggesting that miR-192 may also play a role in other forms of renal disease. More recently, a tight association was observed between upregulation of miR-192 in the fibrotic kidney and TGF-β1/Smad signaling pathways.

**miRNAS IN DIABETIC NEPHROPATHY**

Diabetic nephropathy (DN) is the leading cause of kidney failure, affecting the glomerulus and ultimately leading to progressive kidney scarring. Fibrosis is characterized by the excess accumulation and deposition of extracellular matrix (ECM), the predominant proteins being collagens, but also fibronectin, fibrillin and elastin. ECM is synthesized by many cell types but the principal effector cells in

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**TABLE 1**

| Complication          | Known targets          | Reference |
|-----------------------|------------------------|-----------|
| Diabetic nephropathy  | PTEN (29) unpublished* |           |
| miR-21                |                        |           |
| miR-29 family         | Collagens (25)         |           |
| miR-192               | ZEB2, Col 1 (16,18,22,23) |         |
| miR-93                | VEGF (34)              |           |
| miR-200 family        |                        |           |
| miR-200               | VEGF (34) indirect†    |           |
| Retinopathy           |                        |           |
| miR-93, miR-200, and miR-29 |                |           |
| miR-16                | VEGF, FGF, IGFBP-1, and IGFBP-1 | (34) indirect† |
| Heart                 |                        |           |
| miR-21                | VEGF                   |           |
| miR-29                | VEGF                   |           |
| miR-200 family        |                        |           |

*H.Y.L., unpublished data.†Inferred from the reference.

They made similar observations in hyperglycemic leptin obese mice. Interestingly, they observed the decreased expression of six miRNAs several years prior to the onset of type 2 diabetes. This decreased expression correlated with subclinical peripheral artery disease, suggesting that such a signature may be used to identify high risk individuals prone to getting diabetes complications. Studies such as this are very important and have the potential to make important contributions toward earlier identification of high risk individuals and better management of the early disease. Further advances in profiling techniques using readily accessible biological fluids will lead to good advances in this important area.

The identification of single nucleotide polymorphisms (SNPs) in certain miRNAs (11) and, in particular, in miR-29 in type 1 diabetes is interesting given the potential role of miR-29 in renal fibrosis (see below). Whether these SNPs alter the regulation of miRNA transcription/stability and whether they are relevant on a broader scale in diabetes complications will need to be clarified.

A real advance in this area would be the confirmation of the previously identified miRNA signature (10) and further development to identify prediabetes in patients before they develop overt disease. Equally important would be the identification of a signature for the subset of diabetes patients that go on to develop complications.

**FIG. 1.** Summarized here are the miRNAs known to have a role in the development and progression of diabetic nephropathy. A number of miRNAs have been identified as contributing to diabetes complications and in particular in diabetic nephropathy. Several of the miRNAs shown here have been directly connected to this disease via specific targets, while the specific details of others are yet to be clearly established. In the case of miR-192, the dual published roles are shown.
Smad3 activity and attenuate TGF-$\beta$-mediated signaling. Indeed, overexpression of the miR-192 mimic promoted whereas knockdown of miR-192 inhibited TGF-$\beta$-induced collagen expression.

In contrast to the above, other reports suggest the relationship between miR-192 and renal fibrosis may be more complicated. Krupa et al. (23) identified two miRNAs in human renal biopsies, the expression of which differed by more than twofold between progressors and non-progressors with respect to DN, the greatest change occurring in miR-192 which was significantly lower in patients with advanced DN, correlating with tubulointerstitial fibrosis and low glomerular filtration rate. They also reported, in contrast to the Kato et al. (16) study in MCs, that TGF-$\beta$-1 decreased expression of miR-192 in cultured proximal tubular cells (PTCs) (23). These investigators concluded that a decrease in miR-192 is associated with increased renal fibrosis in vivo. Our own work in this area confirms the view that loss of miR-192 is associated with renal fibrosis (18).

TGF-$\beta$-1 treatment induced decreased expression of miR-192 and miR-215, which target ZEB2, along with changes typical of EMT, including increased fibrogenesis and decreased E-cadherin expression in PTCs. Interestingly, connective tissue growth factor (CTGF) treatment also resulted in fibrogenesis but caused the induction of miR-192/215 and, consequently, decreased ZEB2 and increased E-cadherin. Ectopic expression of miR-192/215 resulted in increased E-cadherin by targeting ZEB2, but had no impact on fibrogenesis. Thus, our work demonstrates a clear link between miRNA-192/215 and ZEB2 in TGF-$\beta$1/CTGF-mediated changes in E-cadherin expression, independent of fibrosis (18).

The contrasting findings above highlight the complex nature of miRNA research. Some of the differences may relate to models and/or experimental conditions; however, one often overlooked explanation is that some effects of miRNAs and inhibitors are likely to be indirect in nature. Our understanding of how miRNAs function is continually evolving, with recent evidence demonstrating that miRNAs can also regulate gene expression via deadenylation and altering message stability, and by modulation of transcription. Bioinformatics using pathway analysis will be needed to better understand the cross-talk between factors that drive many downstream processes and how those processes ultimately impact the expression of individual genes.

The miR-200 family. The next family of miRNAs to become a hot area of research in DN was the miR-200 family with researchers quickly making the obvious link between miR-200 and EMT. The pioneering work of Gregory et al. (14) established the role of the miR-200 family as regulators of the epithelial phenotype primarily by targeting ZEB1/2, the transcriptional repressors of E-cadherin. These observations established the important link between miRNA, the prosclerotic TGF-$\beta$ pathways, and EMT in fibrosis. Both TGF-$\beta$-1 and TGF-$\beta$-2 decreased the expression of the miR-200 family in renal cells (18,19). This decrease is accompanied by an increase in expression of TGFB2, the 3' UTR of this prosclerotic cytokine being a target for miR-200a. This work demonstrated a feedback loop by which increased TGF-$\beta$-2 causes decreased miR-200a, which in turn relieves repression of TGF-$\beta$ expression, and hence promotes fibrosis. Interestingly, we also observed that miR-200a could decrease Smad3 activity and attenuate TGF-$\beta$-induced ECM protein synthesis, however whether this effect was direct was not determined (19).

miR-29. Recent reports have linked miR-29 to fibrosis, especially in renal disease. miR-29a has been shown to be important in the regulation of a number of collagens in a model of hypertensive renal disease (24) and miR-29b in the kidneys of salt-sensitive rats (24). Qin et al. (25) found that miR-29 was downregulated in the fibrotic kidney of obstructive nephropathy and was negatively regulated by TGF-$\beta$-1 via the Smad3, but not the Smad2, signaling pathway. Indeed, Smad3 physically bound the miR-29 promoter and repressed miR-29 expression, thereby promoting collagen matrix expression. Our own unpublished work has also demonstrated significantly decreased expression of miR-29 family members in STZ-induced diabetic mice and rats. More importantly, the finding of inhibition of progressive renal fibrosis in obstructive nephropathy by ultrasound-microbubble–mediated miR-29b gene transfer demonstrated that miR-29 may be a novel therapeutic molecule for renal fibrosis (25).

miR-216a. Kato et al. (26) have proposed miR-216a as another potential contributor to DN. miR-216a was up-regulated by TGF-$\beta$-1 in MCs, resulting in increased col1a2 expression. This involved an interaction between the col1a2 E-box and a complex of a number of molecules, one of which was shown to be regulated by the RNA-binding protein YB-1 (26). Kato et al. (26) postulated that increased miR-216a regulates the expression of Col1a2 by targeting YB-1 expression. Fraser et al. (27) demonstrated that YB-1 is a regulator of TGF-$\beta$-1 mRNA translation in PTCs. Therefore, repression of YB-1 by miR-216a may also significantly contribute to fibrogenesis through increased TGF-$\beta$. miR-216a and miR-217 have also been implicated by targeting the repression of the phosphatase and tensin homolog (PTEN) tumor suppressor gene, which results in activation of Akt, a key driver of DN (15,28). This example demonstrates the indirect and complex pathways by which miRNAs can affect important processes in cell physiology and biochemistry. One needs to add to this scenario the promiscuous nature of miRNAs and the multiple miRNA regulatory sites found on miRNAs to fully appreciate the tremendous complexity of miRNA regulation of cellular processes and disease.

miR-21. Decreased expression of miR-21 has been observed early in DN, while ectopic expression of miR-21 inhibits MC proliferation under conditions of elevated glucose (29). Ectopic expression in vivo resulted in decreased albuminuria in diabetic db/db mice (29). PTEN is a target of and is decreased by miR-21, leading to increased p-Akt in MCs and db/db mice. How the opposing actions of decreased miR-21 (29) and increased miR-216a (15,28), which both target PTEN, contribute to renal fibrosis will need to be clarified. The relative contribution of each miRNA and the overall balance of miRNA expression needs to be established in order to make sense of the published data. Once again the contrasting experimental findings highlight the complex role of miRNAs in disease. We have recently observed that miR-21 expression was significantly upregulated in a mouse model of obstructive nephropathy and was also regulated by the TGF-$\beta$/Smad3 signaling pathway in vivo and in vitro. The findings that overexpression of miR-21 enhanced but that knockdown of miR-21 blocked renal fibrosis in vitro in response to
TGF-β1 and in vivo in a mouse model of obstructive nephropathy suggests that miR-21 may also be an attractive target for the prevention of renal fibrosis under certain conditions (unpublished data, P.K., B.W., R.M.C., and H.Y.L.).

**miR-377.** miR-377 was found to be elevated in spontaneous and STZ-induced models of DN (30). This study also found miR-377 to be elevated in MCs following TGF-β1 treatment in high glucose conditions. Ectopic expression of miR-377 in MCs resulted in increased fibronectin expression as well as other genes that contribute to DN. Fibronectin is not a direct target of miR-377, however miR-377 targets the expression of PAK1 and MnSOD, which indirectly lead to elevated fibronectin expression (30) and hence contribute to DN. The overall contribution of miR-377 to DN remains to be determined.

**miR-93.** Vascular endothelial growth factor (VEGF) has been implicated in microvascular complications and is considered to be a significant player in diabetic retinopathy and nephropathy where it is often upregulated (31,32). Anti-VEGF treatment in animal models of diabetes showed significant improvement in kidney function (33). Long et al. (34) recently identified miR-93 to be a “signature miRNA” in hyperglycemic conditions both in vitro and in vivo, and that VEGF-A was a target of miR-93. They reported that hyperglycemia led to reduced miR-93 expression by downregulating the promoter of the host gene MCM7 in which miR-93 resides. The authors demonstrated that increased miR-93 expression prevented the hyperglycemia-induced expression of VEGF and its downstream signaling. Conversely, targeting miR-93 in vivo with morpholino oligomers induced VEGF expression (34).

### Diabetic Retinopathy

There are currently no studies linking miRNAs to diabetic retinopathy (DR). It is generally believed that the hyperglycemic environment and elevated expression of several growth factors are key mediators of DR. Of particular importance is VEGF which has been shown to be elevated in DR, resulting in pathogenic changes to the retinal structure, including neovascularization (32,35). Anti-VEGF therapy appears to be promising, although the findings of large trials are awaited to confirm these early findings (36). Given that VEGF is a predicted target of several miRNAs, including those that have already been implicated in other diabetes complications (miR-200b/c, miR-29a/b/c, and miR-93), it would be interesting to determine whether these miRNAs may also be relevant in DR.

### Diabetic Atherosclerosis

Advanced glycation end products (AGEs) act through the receptor for AGEs (RAGE), activating inflammatory pathways. One of the endogenous physiological ligands of RAGE is S100b, a member of the S100/calgranulin family (37), and interaction of these ligands with RAGE is critical in inflammation, including in diabetic atherosclerosis (38). Shanmugam et al. (39) recently reported that expression and binding of miR-16 to the COX-2 mRNA 3’UTR in THP-1 monocytic cells was inhibited by the binding of S100b to the RAGE receptor. In this case, the binding of S100b displaced the nuclear heterogeneous nuclear ribonucleoprotein K such that it translocates to the cytoplasm, to interact with the COX-2 3’UTR, to interfere with the binding of miR-16. The complexity of such interactions serves to remind us of the various layers of regulation that need to be understood before our knowledge of miRNAs can be used to produce better therapeutic outcomes in diabetes complications. More recent work has identified increased miR-503 as an important contributor to diabetes-induced impairment of endothelial function and angiogenesis by directly targeting CCNE1 and cdc25A (40). Whether this miRNA plays a role in diabetic atherosclerosis remains to be established.

### Heart

**miR-133.** Diabetic cardiomyopathy, although not fully characterized, typically displays hypertrophy of the heart and contractile dysfunction, which eventually leads to heart failure. Much attention has focused on miR-133, since it is abundantly expressed in heart and is a regulator of myogenesis (41). In the diabetic context, miR-133 has been postulated to be a significant contributor to cardiac pathology. The role of miR-133 in the diabetic heart is very interesting as it appears to have a dual role depending on whether expression is increased or decreased. How the balance between the two opposing actions of miR-133 works in diabetes remains an intriguing mystery.

Elevated cardiac expression of miR-133 is dependent on the serum response factor (SRF), which is elevated in the diabetic heart (42). Knockdown of SRF prevents increased expression of miR-133 (42), and cardiac specific dysregulation of SRF expression results in cardiac hypertrophy and other cardiac pathologies similar to those observed in the early stages of congestive heart failure. One consequence of increased cardiac expression of miR-133 is a perturbation to cardiac conductivity (42). An important electrical disturbance that is seen in diabetic patients is the prolongation of the QT interval, which represents the duration for ventricular depolarization and repolarization of myocytes. This cycle is controlled by the flow of ion currents through K+ channels, which when perturbed result in what is known as the long QT syndrome (LQTS) (42), potentially a life threatening disorder. The rapid delayed rectifier K+ current (IKr) is regulated by the human ERG gene, which is downregulated in cardiac myocytes in diabetes, resulting in prolonged repolarization and therefore long QT syndrome (43). The 3’UTR of the ERG mRNA is a target of miR-133 (42).

Decreased cardiac expression of miR-133 has also been associated with cardiac hypertrophy (44). In this condition, a thickening of the heart muscle results in smaller ventricular size and reduced cardiac output, a phenomenon observed with hypertension, the prevalence of which is increased in subjects with diabetes. Consistent with these observations, overexpression of miR-133 inhibits cardiac hypertrophy whereas inhibition of miR-133 induces more pronounced hypertrophy (44). Indeed, Feng et al. (45) have demonstrated decreased miR-133a in the diabetic mouse heart. Furthermore, in vitro exposure of cardiomyocytes to high glucose resulted in reduced miR-133a and more hypertrophic changes. The genes that are dysregulated in this case are RhoA, Cdc42 and WHSC2, all of which are known to be important in cardiac hypertrophy (44).

**miR-320.** Recent work by Wang et al. (46) identified elevated miR-320 as a potential mediator of several angiogenic factors in diabetic myocardial microvascular endothelial cells as compared with control cells. The factors regulated by this miRNA include VEGF, fibroblast growth factor, IGF-1, and IGF-1R—all of which are particularly relevant to diabetic cardiomyopathy. Increased expression of miR-320
and consequently decreased expression of IGF-1 and IGF-1R are likely to play a role in the impaired angiogenesis observed in diabetes. **miR-29.** The work of van Rooij et al. (17) demonstrated a role for miR-29 in human and mouse hearts during myocardial infarction. Ectopic expression of miR-29b was shown to decrease collagen expression in cardiac fibroblasts. Conversely, miR-29 inhibitors delivered by tail vein injection were able to decrease collagen expression not only in the heart, but also in the liver and kidney. Whether dysregulation of the miR-29 family members occurs in the diabetic heart as in the kidney remains to be established. **miR-30.** CTGF expression is important in the heart where expression levels correlate with collagen levels and fibrosis. Liu et al. (47) reported that miR-133 knockout mice develop severe cardiac fibrosis. Both miR-30 and miR-133 target CTGF for repression (48) and may be relevant since elevated CTGF levels are seen in the context of diabetes, including within the heart (49). **miR-21.** Enhanced expression of miR-21 in the failing heart is selectively expressed in cardiac fibroblasts (50) and is increased in association with elevated extracellular signal-regulated kinase (ERK) signaling by downregulating the ERK inhibitor, Spry1. The ultimate result of activated ERK in cardiac fibroblasts is elevated collagen expression. In vivo silencing of miR-21 caused decreased ERK kinase activity and reduced interstitial fibrosis. Increased expression of miR-21 is found in the infarct zone in cardiac fibroblasts (51). Despite the importance of miR-21 in DN, it remains to be determined how relevant this miRNA is to complications in the diabetic heart.

**WHAT DOES THE FUTURE HOLD?**

Despite considerable progress in further understanding the link between miRNAs, development, physiology, and disease, what is becoming clearer is the ever-increasing complexity of the interactions between miRNAs and mediators of signaling pathways that are relevant to diabetes and particularly to its complications. It is becoming clearer that a number of factors need to be taken into account with miRNA research and that the study of individual miRNAs, which are interesting in their own right, should not be interpreted in isolation. While a number of miRNAs have been associated with diabetes complications (Table 1), the challenge remains to establish the role of these miRNAs in clinical disease and to identify the regulatory mechanisms or pathways related to miRNA expression in the pathogenesis of the various disorders. The development of new genetic miRNA mouse models will greatly facilitate advances in this exciting area and help to address some of the unanswered questions regarding the regulation of signaling pathways that emanate from many of the in vitro observations. There is also much commercial interest in the development of technologies to block or enhance miRNA expression in vivo as a new approach to the management of human disease, including the treatment of diabetes complications.

Two significant challenges remain a barrier to taking advantage of the knowledge currently gained in experimental studies to the next stage where they can be used clinically. In recent times, the focus has moved toward a number of specific miRNAs that are emerging as potential therapeutic targets either by restoring expression or inhibition. Chemical advances in the area of delivery of miRNA inhibitors including cholesterol modifications and locked nucleic acid–modified anti-miRNAs have enabled efficient delivery of these molecules to various tissues (52,53), the stability of the inhibitors ranging up to 10 weeks in vivo following a single injection (17). However, in terms of in vivo delivery of miRNA mimics, huge challenges remain because mimics have a very short half-life and chemical modification alters their biological properties. Much of the literature describing such studies with mimics needs to be carefully evaluated. Some options being investigated include viral mediated delivery of mimics. This approach has been used in different models with a moderate degree of success (44,54–56).

A second obstacle relates to the targeting of specific tissues. Most approaches to date have involved nonspecific systemic delivery. The use of adeno-associated viral serotypes can improve specific delivery to some tissues (57). More recent attention has turned to the development of virally delivered tissue specific promoter driven miRNA expression. The development of therapeutic strategies to effectively deliver the miRNAs or inhibitors into the diseased tissues is urgently needed.

Despite the challenges for miRNAs as either a therapy or a target for new therapies, the use of miRNAs holds much promise as a new treatment, since these molecules are naturally occurring endogenous regulators of cell processes that are often dysregulated in disease. With improved understanding of the mechanisms whereby miRNAs repress gene expression and the development of more selective and stable mimics and inhibitors of miRNAs, this could lead to better approaches to address the “gene expression defects” that occur in various diseases, including diabetes complications. Where dysregulation of specific miRNA expression is linked to disease, the development of better targeted delivery systems is likely to lead to tailored treatment of patients. With the emergence of specific miRNAs that are common to a number of complications such as mir-29, which is implicated in organ fibrosis, the development of a more generalized approach to treat complications with the administration of a small cocktail of miRNAs or inhibitors becomes feasible. Indeed, profiling experiments to identify patterns of miRNA dysregulation that may be common to several complications would be a useful first step in this direction.

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P.K. researched data and wrote the manuscript. B.W. researched data and reviewed the manuscript. R.M.C. researched data and reviewed and edited the manuscript. H.Y.L. researched data and reviewed and edited the manuscript.

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