EM W J

World Journal of *Experimental Medicine*

Submit a Manuscript: https://www.f6publishing.com

World J Exp Med 2018 November 30; 8(3): 18-23

DOI: 10.5493/wjem.v8.i3.18

ISSN 2220-315x (online)

MINIREVIEWS

Circulating microRNAs as biomarkers for diabetic neuropathy: A novel approach

Eleni Xourgia, Athanasia Papazafiropoulou, Andreas Melidonis

ORCID number: Eleni Xourgia (0000-0001-5766-3209); Athanasia Papazafiropoulou (0000-0002-7596-4942); Andreas Melidonis (0000-0003-0505-5708).

Author contributions: All authors equally contributed to this paper with conception and design of the study, literature review and analysis, drafting and critical revision and editing, and final approval of the final version.

Conflict-of-interest statement: No potential conflicts of interest. No financial support.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licen ses/by-nc/4.0/

Manuscript source: Invited manuscript

Corresponding author to:

Athanasia Papazafiropoulou, MD, MSc, PhD, Attending Doctor, 1st Department of Internal Medicine and Diabetes Center, Tzaneio General Hospital of Piraeus, 1 Zanni and Afentouli Street, Athens 18536, Greece. pathan@ath.forthnet.gr **Eleni Xourgia, Athanasia Papazafiropoulou, Andreas Melidonis,** 1st Department of Internal Medicine and Diabetes Center, Tzaneio General Hospital of Piraeus, Athens 18536, Greece

Abstract

Oxidative stress stemming from tissue exposure to constant hyperglycemia is one of the major pathogenetic pathways of diabetic macro- and microvascular complications. Diabetic polyneuropathy, commonly manifesting as distal, symmetrical sensorimotor polyneuropathy, is characterized by progressive severity of symptoms, with rates analogous to the quality of glycemic control achieved by the patients and physicians. Palliative care with analgesics and aggressive glycemic control often improve quality of life in the absence of causative treatment. Currently, there is a growing body of evidence indicating the role of microRNAs in the pathogenesis of diabetic complications, with emphasis on diabetic nephropathy and neuropathy. Therefore, in this review, we aim to explore the role of microRNAs and their polymorphisms in the pathophysiology of diabetic polyneuropathy, as well as, the possibility of novel diagnostic and therapeutic applications by epigenetic profiling and manipulation.

Key words: Diabetic neuropathy; Type 2 diabetes mellitus; Type 1 diabetes mellitus; Epigenetic; MicroRNAs

©The Author(s) 2018. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: In this review, we aim to create a concise overview of the epigenetics underlining the pathogenesis of diabetic neuropathy with emphasis on the altered microRNA expression patterns identified on both animal and human subjects, while, exploring the manner by which they could be manipulated and utilized as novel therapeutic targets.

Xourgia E, Papazafiropoulou A, Melidonis A. Circulating microRNAs as biomarkers for diabetic neuropathy: A novel approach. *World J Exp Med* 2018; 8(3): 18-23 URL: https://www.wjgnet.com/2220-315x/full/v8/i3/18.htm DOI: https://dx.doi.org/10.5493/wjem.v8.i3.18



Telephone: +30-697-996483

Received: October 13, 2018 Peer-review started: October 15, 2018

First decision: November 1, 2018 Revised: November 5, 2018 Accepted: November 15, 2018 Article in press: November 15, 2018 Published online: November 30, 2018

INTRODUCTION

Diabetic neuropathy (DN), a common microvascular complication in type 1 (T1DM) and type 2 diabetes mellitus (T2DM) and is defined as the presence of signs and/or symptoms of peripheral nerve dysfunction in patients with diabetes after the exclusion of other causes^[1,2]. Population and clinical-based studies suggest DN prevalence rates of 20% in T1DM following 20 years of disease duration and approximately 10%-15% at T2DM diagnosis increasing to as high as 50% at 10 years of disease^[3]. Despite the research conducted on the topic, the pathophysiology underlying the process has not been clearly defined, on account of both the numerous intertwining causative mechanisms and the difficulty in establishing a definite diagnosis^[4]. Specifically, the diagnostic approach of DN is complicated rather than standardized, commonly comprising of a combination of various qualitative and quantitative methods in order to increase the sensitivity and specificity of the results.

Additionally, effective screening for early abnormalities preceding the appearance of overt clinical manifestations, patients with asymptomatic disease course, or identification of candidates for the development of DN has not been achieved, to a satisfactory degree, by use of current methods^[5]. In correlation to the lack of a highly reliable diagnostic method for DN, there is a similar degree of complexity concerning the treatment regimens currently in use. In the absence of causative treatment for the development of DN, current therapeutic approach is often comprised of a combination of glycemic control and pain management^[3]. Both the need for development of a high repeatability, non-invasive, diagnostic method and the identification of a possible causative therapeutic approach for DN, allow for consideration the possible use of microRNAs (miRNAs), molecules that have been utilized as biomarkers and focus points of targeted therapy in numerous pathophysiological processes^[6].

Therefore, in the present review, we attempt to summarize the existing literature data on the role of miRNAs and their polymorphisms in the pathophysiology of DN, as well as the possibility of utilizing the aforementioned research for novel diagnostic and therapeutic applications by means of epigenetic profiling and manipulation.

CIRCULATING MIRNAS AS BIOMARKERS AND THERAPEUTIC TARGETS

MiRNAs are small, non-coding RNA sequences with a regulatory role in posttranscriptional modification of gene products. Structurally, they comprise of 18-24 nucleotides in length that are organized in a partially complementary manner to cellular mRNA molecules. MiRNAs bind to mRNAs *via* base pairing and induce various changes to the latter, ranging from destabilization to cleavage of the molecule. Alternatively, the mRNA-ribosome complex formation is disrupted by miRNA interference, resulting into similar deregulation of the normal protein formation sequence^[7]. Various cellular and tissue types have been shown to express miRNAs as part of their metabolic, developmental and homeostatic processes^[8].

It has long been established that the prospect of utilizing circulating miRNAs as diagnostic and therapeutic tools could provide substantial insight into the mechanisms underlining numerous disease processes, as well as become the substrate for therapeutic advances in multifactorial disease states^[6]. Currently, novel prospects are being explored concerning the utility of miRNA measurement in the clinical setting, such as assessing response to treatment or disease activity^[7].

Researchers have isolated stable miRNA molecules from various tissue types including human plasma, indicating the ability for genetic profiling by use of blood samples, a process far more accessible and easily conducted on both in- and outpatient setting than tissue biopsy^[9]. The possible value of miRNA profiling in DN is supported by the fact that mapping of aberrant miRNA expression has been performed in both nervous system and metabolic disorders, along with the observation that most of the currently discovered miRNAs are located in the brain and peripheral neural tissue^[9].

Simultaneously to new details for miRNA aberrant expression patterns in disease constantly being unveiled, current methods for epigenetic manipulation of target genes are being ameliorated. The two main approaches to miRNA centered therapy are substitution of under-expressed or otherwise modified miRNAs with functional copies designed *ex vivo*, termed miRNA mimics, or delivery of small molecules, in vivo, that disrupt the pathophysiological cellular pathways in which the target genes participate. Both miRNA mimics and inhibitors have been delivered at the target tissues by use of numerous conjugate molecules in the experimental setting^[9]. The

anishideng® WJEM | https://www.wjgnet.com

main delivery platforms are subdivided into two categories, non-viral and viral, with the latter harboring many safety concerns. Some of the non-viral molecules are cationic polymers, various conjugates and liposomes, with neutral lipid particles having a more balanced organ-wide distribution than cationic complexes, resulting in less unwanted accumulation in certain tissues. Exosomes and bacteriophages, while being efficient delivery platforms, have the possibility of triggering adverse events such as immune dysregulation and are, therefore, not the vectors of choice^[10].

The integration of miRNA-centered treatments in real-world conditions is progressing rapidly, with several clinical trials currently underway^[11].

MIRNAS IN DIABETES MELLITUS AND METABOLIC DYSREGULATION

Aberrant expression of miRNAs in tissue and plasma samples has been linked to the pathogenesis of several metabolic diseases, mainly because of their role in the development and homeostasis of metabolically active tissues.

Ample evidence has suggested the involvement of disrupted miRNA expression patterns in metabolic dysregulation. While the spectrum of metabolic disease is wide and includes many, often overlapping, syndromes and pathological states, some prime examples of aberrant tissue miRNA expression include those of miRNA-15b in non-alcoholic fatty liver disease, miRNA-744 in non-alcoholic steatohepatitis, miRNA-132-3p in obesity and miRNAs -30b, -455, -491 and -365-3p in pathological adipose tissue differentiation^[12].

MiRNAs from many tissue types involved in diabetes have been linked to many components of the disease state. Several pancreatic, cardiac, liver, kidney, skeletal, endothelial and adipose tissue miRNAs interact directly or indirectly with β -cell pathophysiology, inducing or suppressing pathways involved in lipid metabolism and adipocyte differentiation (miRNA-181d, -27a/b, -103, - 107, -143), insulin resistance, glucose-mediated insulin secretion and exocytosis (miRNA-29a/b/c, -375, -9, -124a, -96, -34a, -30d, -223, -320, -21), β -cell development, apoptosis and function (miRNA-375, -9, -195, -126, -296, -34a, -146b, -21) cardiomyocyte apoptosis and cardiac arrythmiogenesis (miRNA-206, -1, -133a), endothelial dysfunction and angiogenesis (miRNA-93, -320, -125a/b) and glomerular activity (miRNA-192, -216a, -217)^[13].

Further, disease-specific research on diabetics and more specifically, profiling of circulating miRNAs as predictors for T2DM or prediabetes in healthy subjects indicated the existence of a link between higher plasma levels of miRNA-150 and miRNA-30a-5p, and lower levels of miRNA-375 and miRNA-15a at baseline and disease development after a median follow-up of 60 mo^[14].

Similarly, to miRNA-15a, the expression of several other circulating molecules has been found to be down- or upregulated in plasma samples of T2DM subjects. La Sala *et al*^[15] note that miRNAs -20b, -21, -24, -126, -191, -197, -223, -320 and -486 in T2DM plasma samples are present in lower concentrations when compared to healthy controls, while miRNA-28-3p in upregulated. Among the aforementioned miRNAs, -15a, -28-3p, -126, -223 and -320 have been proposed for possible use as biomarkers of T2DM.

Additionally, recent data acquired from analysis of various expression patterns of quantitative trait loci in mouse inbred strains with varying susceptibility to metabolic dysregulation and T2DM development has indicated an upregulation of miRNA-31 in adipose tissue of obese and type 2 diabetic subjects. MiRNA-31 interacts with genes of the insulin signaling pathway and adipose tissue proliferation^[12].

MIRNAS AS BIOMARKERS IN DIABETIC NEUROPATHY: WHY, WHICH AND WHEN?

The most important problem posed when discussing a novel treatment possibility in the clinical setting is the clarification of the circumstances under which a new interventional approach should be applied, or, in simpler terms, the evaluation of the cost-effectiveness of the method. In the setting of DN, the two pivotal arguments in favor of epigenetic modification are the lack of causative treatment for a major complication of a chronic disease with a high prevalence and the enormous impact of DN on the patients' quality of life, an indisputable fact that has been repeatedly documented^[3,16].

Researchers on the field of epigenetics have provided insight on some miRNA molecules that could be evaluated as possible biomarkers or therapeutic targets in

diabetes-induced neuropathy. A study including 60 diabetic subjects revealed a correlation between miRNA-199a-3p and reduced expression of extracellular serine protease inhibitor E2 resulting in DN manifestation and accelerated progression^[17]. A similar pathway has been described, involving miRNA-190a-5p downregulation and resultant impaired solute carrier family 17 member 6 gene inhibition in painful DN^[18]. Conversely, medically induced downregulation of miRNA-25 exacerbated the development of DN via an increase of advanced end glycation products and their receptors in peripheral neural tissue, indicating the neuroprotective attributes of miRNA-25 molecules^[19]. In an experimental model on diabetic rodents, miRNA-9 and its interaction with calcium homeostasis modulator 1 were suggested to be involved in the pathophysiological pathway of painful DN^[20]. MiRNA-146 located in circulating mononuclear cells modulates inflammatory response in diabetic peripheral neuropathy^[21,22]. DN painful manifestation and inflammatory response are also affected by miRNA-23a via chemokine CXC receptor 4-related signaling^[23]. Recent data indicate that a certain genotype termed "GG" in miRNA499A has been linked to cardiovascular autonomic neuropathy as well as diabetic polyneuropathy^[24]. Finally, substantial upregulation of miRNA-29c and subsequent protein kinase C iota gene under-expression have been associated with distal neural damage in a model of diabetic rodents^[25]. A brief comparison of all relevant to DN miRNAs discussed above is presented in Table 1. Circulating molecules can be used more readily as biomarkers when compared to tissue-derived molecules.

Even with the existence of an abundance of possible biomarkers and therapeutic targets, as indicated by the research described above, the timeframe in which predisposition for DN development can be detected or DN can be treated is yet to be defined. While it is expected that miRNA aberrant expression patterns precede the clinical manifestation of DN, the elucidation of the exact timeline describing when these changes occur and can be detected in the research setting in advance is of uttermost importance in the design of effective intervention algorithms for complication prevention. When miRNA manipulation is examined in the scope of neuropathy treatment, it should be studied whether miRNA expression normalization can reverse damage already done to the neural tissue or impede the progression of sensory and motor deterioration. Furthermore, the particular points in disease progression appropriate for treatment initiation or termination can be defined, based on treatment efficacy at different stages and forms of disease.

CONCLUSION

MiRNA-based diagnosis and therapy are highly likely to be the future of treatment and prevention, especially in multifactorial disease processes. The transition from theory to practice, while an ongoing process, is rapidly progressing, with several molecules being used in clinical trials and many more currently on the preclinicalstage. While DN is the result of several complex pathophysiological processes, several miRNA molecules involved and their role have been described, setting the stage for the practical application of the aforementioned information. A next step in the development of miRNA-based diagnosis, staging and therapy is examining the miRNAs so far associated with neuropathy and diabetes in a prospective cohort study including diabetic subjects free of complications, with the goal of evaluating miRNA epigenetic changes accumulating over time in correlation with the appearance and severity of DN. Current available research data indicate that miRNAs -199a-3p, -146 and -499a can be used as circulating biomarkers, while the aforementioned along with miRNAs -190a-50, -25, -9, -23a and -29c have potential as therapeutic targets in DN.



miRNA-29c

Table 1 Possible biomarkers and therapeutic targets in diabetic neuropathy MiRNA molecule Mechanism Expression in DN Circulating Citation [17] miRNA-199a-3p Inhibition of SerpinE2 Upregulated Yes expression - coagulation in peripheral circulation [18] miRNA-190a-5p Inhibition of SLC17A6 gene Downregulated No [19] miRNA-25 Inhibition of oxidative stress. Downregulated No decreases AGEs and RAGE production [20] miRNA-9 Interacts with CALHM1 in Upregulated No neuron-glial signalling [21,22] Interacts with NF_KB and Downregulated miRNA-146 Yes inflammatory cytokines production [23] Targets CXCR4 - regulates miRNA-23a Downregulated No neuropathic pain [24] miRNA499A Upregulated (GG genotype Prevents cardiomyocyte Yes apoptosis and mitochondrial with rs3746444) fission (impaired in cardiac autonomic neuropathy); regulates insulin resistance [25]

MiRNAs: microRNAs; CALHM1: Calcium homeostasis modulator 1; AGEs: Advanced end glycation products; RAGE: Receptor of advanced end glycation product; SerpinE2: Serine protease inhibitor E2; SLC17A6: Solute carrier family 17 member 6; PRKCI: Protein kinase C iota.

Upregulated

REFERENCES

Inhibits neural axonal growth

via inhibiting PRKCI gene expression

> Vileikyte L, Leventhal H, Gonzalez JS, Peyrot M, Rubin RR, Ulbrecht JS, Garrow A, Waterman C, Cavanagh PR, Boulton AJ. Diabetic peripheral neuropathy and depressive symptoms: the association revisited. *Diabetes Care* 2005; 28: 2378-2383 [PMID: 16186266 DOI: 10.2337/DIACARE.28.10.2378]

No

- 2 Kiadaliri AA, Najafi B, Mirmalek-Sani M. Quality of life in people with diabetes: a systematic review of studies in Iran. J Diabetes Metab Disord 2013; 12: 54 [PMID: 24354933 DOI: 10.1186/2251-6581-12-54]
- 3 Pop-Busui R, Boulton AJ, Feldman EL, Bril V, Freeman R, Malik RA, Sosenko JM, Ziegler D. Diabetic Neuropathy: A Position Statement by the American Diabetes Association. *Diabetes Care* 2017; 40: 136-154 [PMID: 27999003 DOI: 10.2337/dc16-2042]
- 4 Schreiber AK, Nones CF, Reis RC, Chichorro JG, Cunha JM. Diabetic neuropathic pain: Physiopathology and treatment. World J Diabetes 2015; 6: 432-444 [PMID: 25897354 DOI: 10.4239/wjd.v6.i3.432]
- 5 Petropoulos IN, Ponirakis G, Khan A, Almuhannadi H, Gad H, Malik RA. Diagnosing Diabetic Neuropathy: Something Old, Something New. *Diabetes Metab J* 2018; 42: 255-269 [PMID: 30136449 DOI: 10.4093/dmj.2018.0056]
- 6 Ajit SK. Circulating microRNAs as biomarkers, therapeutic targets, and signaling molecules. Sensors (Basel) 2012; 12: 3359-3369 [PMID: 22737013 DOI: 10.3390/s120303359]
- 7 Papaconstantinou I, Kapizioni C, Legaki E, Xourgia E, Karamanolis G, Gklavas A, Gazouli M. Association of miR-146 rs2910164, miR-196a rs11614913, miR-221 rs113054794 and miR-224 rs188519172 polymorphisms with anti-TNF treatment response in a Greek population with Crohn's disease. World J Gastrointest Pharmacol Ther 2017; 8: 193-200 [PMID: 29152405 DOI: 10.4292/wjgpt.v8.i4.193]
- 8 **Bartel DP**. MicroRNAs: genomics, biogenesis, mechanism, and function. *Cell* 2004; **116**: 281-297 [PMID: 14744438 DOI: 10.1016/S0092-8674(04)00045-5]
- 9 Wang J, Chen J, Sen S. MicroRNA as Biomarkers and Diagnostics. J Cell Physiol 2016; 231: 25-30 [PMID: 26031493 DOI: 10.1002/jcp.25056]
- 10 Baumann V, Winkler J. miRNA-based therapies: strategies and delivery platforms for oligonucleotide and non-oligonucleotide agents. *Future Med Chem* 2014; 6: 1967-1984 [PMID: 25495987 DOI: 10.4155/fmc.14.116]
- 11 Chakraborty C, Sharma AR, Sharma G, Doss CGP, Lee SS. Therapeutic miRNA and siRNA: Moving from Bench to Clinic as Next Generation Medicine. *Mol Ther Nucleic Acids* 2017; 8: 132-143 [PMID: 28918016 DOI: 10.1016/j.omtn.2017.06.005]
- 12 Gottmann P, Ouni M, Saussenthaler S, Roos J, Stirm L, Jähnert M, Kamitz A, Hallahan N, Jonas W, Fritsche A. A computational biology approach of a genome-wide screen connected miRNAs to obesity and type 2 diabetes. *Mol Metab* 2018; **11**: 145-159 [PMID: 29605715 DOI: 10.1016/j.mol-met.2018.03.005]
- 13 Fernandez-Valverde SL, Taft RJ, Mattick JS. MicroRNAs in β-cell biology, insulin resistance, diabetes and its complications. *Diabetes* 2011; 60: 1825-1831 [PMID: 21709277 DOI: 10.2337/db11-0171]
- 14 **Jimenez-Lucena R**, Rangel-Zuniga OA, Alcala-Diaz JF, Roncero-Ramos I, Yubero-Serrano EM, Perez-Martinez P, Camargo A, Lopez-Miranda J. A plasma circulating miRNAs profile predicts

type 2 diabetes mellitus and prediabetes: From the cordioprev study. *Atherosclerosis* 2018; **275**: e5 [DOI: 10.1016/j.atherosclerosis.2018.06.898]

- 15 La Sala L, Micheloni S, De Nigris V, Prattichizzo F, Ceriello A. Novel insights into the regulation of miRNA transcriptional control: implications for T2D and related complications. *Acta Diabetol* 2018; 55: 989-998 [PMID: 29732466 DOI: 10.1007/s00592-018-1149-4]
- Quattrini C, Tesfaye S. Understanding the impact of painful diabetic neuropathy. *Diabetes Metab Res Rev* 2003; 19 Suppl 1: S2-S8 [PMID: 12577252 DOI: 10.1002/dmrr.360]
 Li YB, Wu Q, Liu J, Fan YZ, Yu KF, Cai Y. miR199a3p is involved in the pathogenesis and
- 17 Li YB, Wu Q, Liu J, Fan YZ, Yu KF, Cai Y. miR199a3p is involved in the pathogenesis and progression of diabetic neuropathy through downregulation of SerpinE2. *Mol Med Rep* 2017; 16: 2417-2424 [PMID: 28677735 DOI: 10.3892/mmr.2017.6874]
- 18 Yang D, Yang Q, Wei X, Liu Y, Ma D, Li J, Wan Y, Luo Y. The role of miR-190a-5p contributes to diabetic neuropathic pain via targeting SLC17A6. J Pain Res 2017; 10: 2395-2403 [PMID: 29042815 DOI: 10.2147/JPR.S133755]
- 19 Zhang Y, Song C, Liu J, Bi Y, Li H. Inhibition of miR-25 aggravates diabetic peripheral neuropathy. *Neuroreport* 2018; 29: 945-953 [PMID: 29877948 DOI: 10.1097/WNR.00000000001058]
- 20 Liu W, Ao Q, Guo Q, He W, Peng L, Jiang J, Hu X. miR-9 Mediates CALHM1-Activated ATP-P2X7R Signal in Painful Diabetic Neuropathy Rats. *Mol Neurobiol* 2017; 54: 922-929 [PMID: 26781424 DOI: 10.1007/s12035-016-9700-1]
- 21 Feng Y, Chen L, Luo Q, Wu M, Chen Y, Shi X. Involvement of microRNA-146a in diabetic peripheral neuropathy through the regulation of inflammation. *Drug Des Devel Ther* 2018; 12: 171-177 [PMID: 29398906 DOI: 10.2147/DDDT.S157109]
- 22 Wang GF, Xu N. Expression and clinical significance of microRNA 146a in peripheral blood mononuclear cells from type 2 diabetic neuropathy patients. *Int J Clin Exp Med* 2018; 11: 7165-7173 Available from: URL: http://www.ijcem.com/files/ijcem0067527.pdf
- 23 Pan Z, Shan Q, Gu P, Wang XM, Tai LW, Sun M, Luo X, Sun L, Cheung CW. miRNA-23a/CXCR4 regulates neuropathic pain via directly targeting TXNIP/NLRP3 inflammasome axis. J Neuroinflammation 2018; 15: 29 [PMID: 29386025 DOI: 10.1186/s12974-018-1073-0]
- 24 Ciccacci C, Latini A, Greco C, Politi C, D'Amato C, Lauro D, Novelli G, Borgiani P, Spallone V. Association between a MIR499A polymorphism and diabetic neuropathy in type 2 diabetes. J Diabetes Complications 2018; 32: 11-17 [PMID: 29108839 DOI: 10.1016/j.jdiacomp.2017.10.011]
- 25 Jia L, Wang L, Chopp M, Li C, Zhang Y, Szalad A, Zhang ZG. MiR-29c/PRKCI Regulates Axonal Growth of Dorsal Root Ganglia Neurons Under Hyperglycemia. *Mol Neurobiol* 2018; 55: 851-858 [PMID: 28070856 DOI: 10.1007/s12035-016-0374-5]

P- Reviewer: Senol MG, Kravtsov V S- Editor: Dou Y L- Editor: A E- Editor: Bian YN







Published By Baishideng Publishing Group Inc 7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA Telephone: +1-925-2238242 Fax: +1-925-2238243 E-mail: bpgoffice@wjgnet.com Help Desk: https://www.f6publishing.com/helpdesk https://www.wjgnet.com

