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MicroRNA-146a expression and its intervention in NF-κB signaling pathway in diabetic rat aorta

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Objective. The present study was designed to evaluate whether microRNA-146a, as an NF-κB regulating factor and its adapter proteins (TRAF6 and IRAK1), are affected by diabetes in rat aorta.

Methods. Male Wistar rats were randomly divided into control and diabetic groups (n=6 in each). Diabetes was induced by a single injection of streptozotocin (55 mg/kg; i.p.) in 12 h fasted rats. The gene expression of microRNA-146a, NF-κB, IRAK1, and TRAF6 were determined by real time PCR.

Results. The expression of microRNA-146a was down-regulated in diabetic aorta when compared with the control group ($p<0.05$). The mRNA expression levels of NF-κB, TRAF6 and IRAK1 also increased in the diabetic rat aorta when compared with their control counterparts ($p<0.01$ for all comparisons).

Conclusion. These results suggest that down-regulation of microRNA-146a may lead to derangement in NF-κB negative feedback loop, propelling the aorta toward inflammation.

Key Words: diabetes, aorta, microRNA-146a, NF-κB, IRAK1, TRAF6

About two decades ago, a typical line of mRNAs was detected, transcribed from mRNA, and contained very little nucleotides. It was therefore called "microRNAs or miRs" (Angulo et al. 2012; Chen et al. 2012; Xu et al. 2012). These noncoding single strand RNAs remain severely conserved during evolutionary and play significant roles in cell proliferation, differentiation, senescence, and apoptosis by regulating the gene expression of many proteins at post-transcriptional levels (Feng et al. 2011; Kin et al. 2012; Sun et al. 2012; Yamakuchi 2012). There is substantial evidence that miRs play an important role in the pathological processes including inflammation, cancer, and atherosclerosis (Schroen and Heymans 2011; Kin et al. 2012). It has been estimated that 60% of human proteins encoding genes were regulated by miRs mostly through genes silencing (Quinn and O'Neill 2011; Yamakuchi 2012). It is believed that miRs dysregulation in many cells results in an unlimited inflammation (Quinn and O'Neill 2011). Diabetes is an inflammatory disorder that changes some miRs expression levels (Yamakuchi 2012), so that some miRs have been recently utilized as diabetes diagnosis biomarkers (Schroen and Heymans 2011). It has been reported that high glucose milieu may induce over or under expression of detrimental or beneficial miRs, thereby contributing to the development of vascular complications (Roberts and Porter 2013). Intervention in Toll-like receptors (TLRs) signaling pathway is one of the mechanisms by which inflammatory miRs exert their role in progression of inflammation (Kovacs et al. 2011; Olivieri et al. 2013). The evidence

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has indicated many miRs, especially miR-146a activates TLRs (Quinn and O'Neill 2011; Schroen and Heymans 2011; Xu et al. 2012). Indeed, miR-146 was first identified as an immune system regulator in a systematic effort to find miRNAs that influence the mammalian response to microbial infection (Baltimore et al. 2008). Importantly, two key adapter proteins in the TLRs pathway, TRAF6 and IRAK1, are identified as direct targets of miR-146 (Zhao et al. 2013).

Nuclear factor kappa B (NF-κB), a nuclear transcription factor that is detectable in all cell types, regulates the expression of many genes in impressive stressful conditions on cells (Patel and Santani 2009; Vereecke et al. 2009). An instance of this occasion has been observed in aorta exposed to hyperglycemia that thereby increased NF-κB activity (Gao et al. 2006; Van den Oever et al. 2010). It has been widely documented that sustained hyperglycemia leads to overproduction and accumulation of advanced glycation end products, reactive oxygen/nitrogen spices, and polyols as well as activates protein kinase C (PKC) and hexosamines pathways. These factors, in turn, converge to activate (NF-κB) to produce its downstream pro-inflammatory cytokines (including TNF-α, IL-1β and IL-6) which activate TLRs (Drimal et al. 2008; Soufi et al. 2012a). It has been suggested that as a negative regulatory loop, NF-κB activation up-regulates miR-146a gene that upon processing and maturation, down-regulates IRAK1 and TRAF6 to reduce the activity of NF-κB (Pacifico et al. 2010; Boldin et al. 2011; Mann 2011; Labbaye and Testa 2012; Cheng et al. 2013).

Dysregulation of miR-146a expression has been observed in many vascular diseases including abdominal aortic aneurysm, atherosclerosis, and coronary artery disease (Schroen and Heymans 2011; Chen et al. 2012; Kin et al. 2012). One of the tissues in which miR-146a and NF-κB expression levels affected by inflammatory processes were found, is aorta (Gao et al. 2006; Van den Oever et al. 2010; Paik et al. 2011). Therefore, to evaluate the changes of these factors during diabetes, we measured miR-146a expression in diabetic aorta and its intervention in NF-κB signaling pathway.

Material and Methods

Experimental design. Male Wistar rats (Razi Institute, Tehran, Iran) weighing 325 - 340 g were housed at room temperature (22 - 25°C) with 12:12 h light/dark cycles and free access to food and water. The study protocol was designed in accordance with NIH (U.S.A.) guidelines for the care and use of laboratory animals approved by ethical committee of the Faculty of Medicine, Tabriz University of Medical Sciences, Iran. All the manipulations were done in the morning. Rats were randomly divided into control and diabetic groups (6 in each). Diabetes was induced by a single injection of STZ (55 mg/kg; i.p.) dissolved in 0.1 M of citrate buffer (pH 4.5) in 12 h fasted rats. Control rats with citrate buffer injection were considered as control counterparts. After 48 h, blood glucose levels were measured using a glucometer (Arkray, Kyoto, Japan) and the rats with blood glucose levels higher than 250 mg/dl were counted diabetic rats (Soufi et al. 2012b). Two months after induction of diabetes, fasted rats were anesthetized with ketamine (80 mg/kg) and blood samples (3 ml per rat) were collected from the retro-orbital sinus. After chest opening, the aorta was quickly removed, weighed and expression of miR-146a, NFkB, IRAK1 and TRAF6 were determined by real time PCR.

Total RNA extraction and real time PCR. Total RNA (including mRNA and microRNA) was extracted from aortic tissue using miRCURY™ RNA isolation kit (Exiqon, Vedbaek, Denmark) according to the manufacturer's protocol (Lasser et al. 2012). The procedure was performed based on spin column using a proprietary resin as a separation matrix for RNA from other cell components. RNA content and purity were measured using Nanodrop 1000 spectrophotometer (Thermo scientific, Wilmington, DE 19810 USA). The expression profile of miR-146a was performed on total RNA extracted by using the universal cDNA synthesis kit. Briefly, total RNA containing miRNA was poly adenylated and cDNA was synthesized using a poly (T) primer with a 30 degenerate anchor and a 50 universal tag (Exiqon, Vedbaek, Denmark). RevertAid First Strand cDNA Synthesis Kit (FermentasGmBH, Leon-Rot, Germany) with aid of random hexamer primers and MMLV reverse transcriptase (as a complete system for efficient synthesis of first strand cDNA from mRNA or total RNA templates) were used for determination of IRAK1, TRAF6 and NF-κB mRNA expression levels.

Each cDNA was used as a template for separate assay for miR-146a and the mRNAs quantitative real-time PCR by using SYBR Green master mix (Exiqon, Vedbaek, Denmark). LNA (Locked Nucleic Acid) forward and reverse Primer sets (Exiqon, Vedbaek, Denmark) for miR-146a and the mRNAs are listed in Table 1. Real-time PCR reactions were performed on a Bio-Rad iQ5 detection System (Bio-Rad, Richmond, CA, USA). The amount of PCR products was normalized with housekeeping beta-glucuronidase gene for the mRNA samples (Fink et al. 2008) and rno-miR-191 for miR-146a (Peltier and Latham 2008). The $2^{-(\Delta\Delta Ct)}$ method was used

to determine relative-quantitative levels of individual mRNAs and miR-146a. The results were expressed as the fold-difference to the relevant controls.

Data analysis. Data were expressed as the mean ± SD and were analyzed by Independent t test using SPSS 18 software. A level of $p<0.05$ was considered statistically significant difference.

Results

Morphological data from the diabetic and control rats revealed that while the body weight of diabetic rats was significantly lower than the control group (220.28 ± 5.01 vs. 469.33 ± 3.88; $p<0.01$), the heart weight and the heart to body weight ratio (as an index of cardiomyopathy) were significantly greater in the diabetic rats than their control counterparts (1.05 ± 0.08 vs. 0.90 ± 0.04; $p<0.05$ and 4.76 ± 0.73 vs. 1.91 ± 0.44; $p<0.01$, respectively).

Two months after uncontrolled diabetes, fasting blood glucose was significantly higher (507.33 ± 4.27 vs. 111.18 ± 4.09; $p<0.01$) and fasting plasma insulin was significantly lower in the diabetic group than the control rats; $p<0.01$).

The expression of aorta miR-146a and the mRNA levels of IRAK1, TRAF6 and NF-κB are presented in Fig. 1. As shown in Fig. 1a, the miR-146a expression level was significantly decreased in diabetic aorta compared to the nondiabetic rats ($p<0.05$). Fig. 1b indicates that the mRNA level of NF-κB in diabetic rats was significantly higher than their control counterparts ($p<0.01$). In association with NF-κB overexpression in the diabetic rats aorta, the IRAK1 and TRAF6 mRNA expression levels also were significantly increased as compared to the nondiabetic group (Fig. 1c and Fig. 1d; $p<0.01$ for both comparisons).

Discussion

The main findings of this study are marked down-regulation of miR-146a and significant overexpression of NF-κB, TRAF6, and IRAK1 mRNAs in diabetic aorta two months after uncontrolled diabetes. Based on the literature, hyperglycemia can alter some intracellular signaling pathways through PKC activation, ROS regeneration and receptor for advanced location end products activation in the vascular cells, including aorta (Berg and Scherer 2005; Gao et al. 2006; Paik et al. 2011; Paneni et al. 2013). Majority of cellular mechanisms resulted from hyperglycemia, unanimously, activate NF-κB (Berg and Scherer 2005; Gao et al. 2006; Soufi et al. 2012a; Paneni et al. 2013). NF-κB is detectable in all cell types and is inactive during cell resting by binding to inhibitory kinase B (IkB) (Cheng et al. 2013). Upon cell exposure to stressors, inhibitory kinases (Ikks) phosphorylate IkB, whereby releases NF-κB which in turn, regulates target genes through positive and negative feedback loops (Sanz et al. 2010; Cheng et al. 2013). It has been documented that NF-κB activation induces miR-146a expression (Chen et al. 2012). The

Table 1

Primer set list for mRNAs and miRNAs

Gene name	Accession number	Primer sequence[a]	
Nfkb1	XM_342346.4	Sense: 50-AATTGCCCCGGCAT-30 Antisense: 30-TCCCGTAACCGCGTA-50	
Irak1	NM_001127555.1	Sense: 50-GCTGTGGACACCGAT-30 Antisense: 30-GCTACACCCATCCACA-50	
Traf6	NM_001107754.2	Sense: 50-CAGTCCCCTGCACATT-30 Antisense: 30-GAGGAGGCATCGCAT-50	
Beta Gusb	NM_017015.2	Sense: 50-GGCTCGGGGCAAATT-30 Antisense: 30-GGGGCAGCACGAT- 50	
Gene name	**Accession number**	**Target sequence[b]**	**Product name**
rno-miR-146a	MIMAT0000449	UGAGAACUGAAUUCCAUGGGUU	hsa-miR-146a, LNA PCR primer set, UniRT
rno-miR-191	MIMAT0000440	CAACGGAAUCCCAAAAGCAGCUG	hsa-miR-191, LNA PCR primer set, UniRT

[a] Sequences were derived from NCBI (www.ncbi.nlm.nih.gov)
[b] Sequences were derived from miRBase (www.mirbase.org)

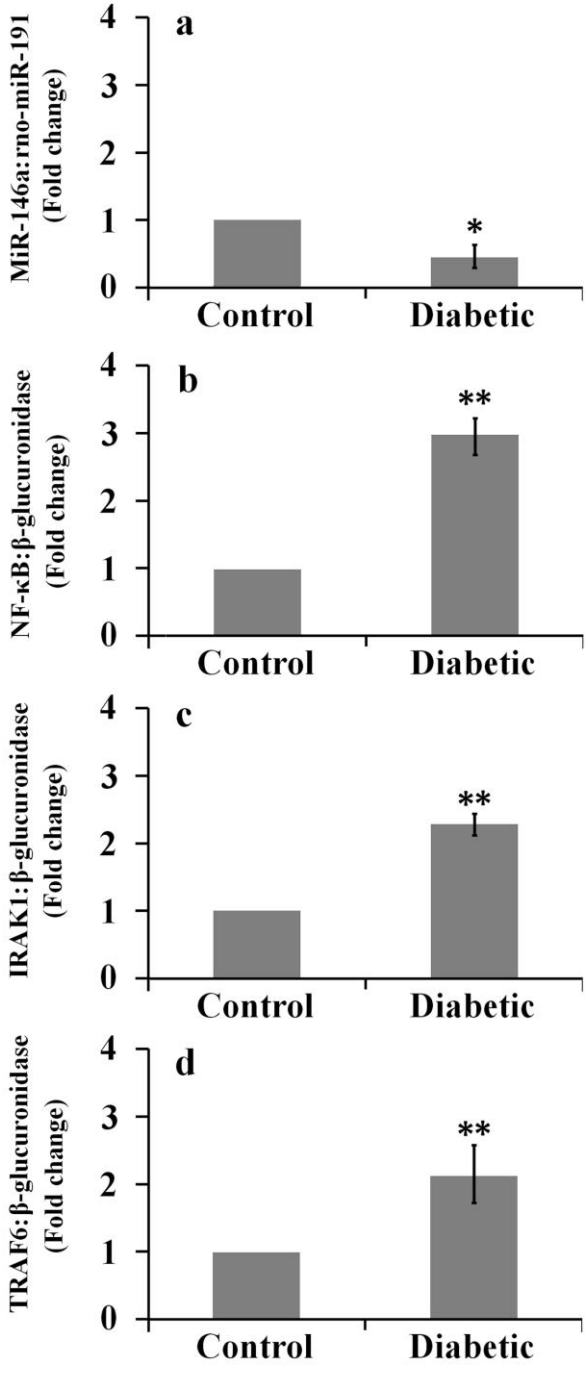

Fig. 1. Real-time quantitative RT-PCR analysis of miR-146a (a) and mRNA expression levels of NF-κB (b), IRAK1 (c) and TRAF6 (d) in the aorta of diabetic and control rats. Data are presented as mean ± SD (n=6); * p<0.05; ** p<0.01 vs. controls.

evidence implicates miR-146a existence in the inflammation conditions in tissues including rheumatoid arthritis, osteoarthritis, and developing myeloid cells, which mainly acts as a negative regulator (Boldin et al. 2011; Quinn and O'Neill 2011). While miR-146a overexpression has reverse effect in some cases, its expression in macrophages leads to inflammatory responses (Boldin et al. 2011). As it has been previously mentioned, TLR ligands are important activators of miR-146a (Quinn and O'Neill 2011). TRAF6 and IRAK1 attend in TLR signaling pathway that activates Ikk and following NF-κB release (Mann 2011; Vaz et al. 2011). It has been proposed that during inflammatory processes, NF-κB regulates itself activation in part via a negative feedback loop in which NF-κB activation upregulates miR-146a gene that upon processing and maturation down-regulates IRAK1 and TRAF6 (two key adapter molecules downstream of cytokine and TLR) to reduce the activation of NF-κB (Lovis et al. 2008; Ma et al. 2011).

Although the anti-inflammatory property of miR-146a has been shown by several reports, the above mentioned negative loop has not been shown by any investigations. For example, Zilahi et al. (2012) have reported over expression of miR-146a and TRAF6 with concomitant reduced expression of IRAK1 in the peripheral mononuclear cells of patients with Sjogren syndrome. We have also previously reported that the up-regulation of miR-146a was not accompanied with down-regulation of IRAK1 and TRAF6 in rat diabetic kidney (Alipour et al. 2013).

In overall, while dysregulation of miR-146a in some inflammatory diseases and in some diabetic tissues has been previously reported, this is the first presentation of data on down-regulation of miR-146a in diabetic aorta with significant up-regulation of IRAK1 and TRAF6. Feng et al. (2011) have previously shown down-regulation of miR-146a in the kidney of type 1 and type 2 diabetic rats. At present, the cause of different behavior of miR-146a in different tissues is unclear. It is also unknown whether miR-146a dysregulation is causal to diabetes or is a consequence of it. However, its action may depend on tissue type, blood and tissue cytokines concentrations, timing, and duration of inflammation.

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