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REVIEW

p53/microRNAs signaling in the pathological mechanism of diabetic kidney disease

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Recent studies found that high glucose increases the expression of tumor suppressor factor p53. And in the process of diabetic kidney disease (DKD) development p53 involves in regulating multiple signaling pathways. In addition, microRNAs (miRNAs) involve in many diseases pathogenesis. And miRNAs affect DKD development via adjusting multiple mechanisms. More importantly, p53/miRNAs signaling may participate in a variety of signaling pathways regulating kidney inflammation and fibrosis to control DKD pathological development. However, the mechanism of p53/miRNAs signaling participating in DKD pathological development is not yet clear. To illuminate the role of p53/miRNAs signaling may inspire a new thinking for elucidating the pathological mechanism of DKD, and provide a new theoretical basis for the prevention and treatment of DKD.

Keywords: p53; microRNAs; diabetic kidney disease

Abbreviations: DKD, diabetic kidney disease; miRNAs, microRNAs; T2DM, type 2 diabetes mellitus; TGF-β1, transforming growth factor-β1; SIRT1, Sirtuin 1; NF-κB p65, nuclear factor κB p65; FoxO, forkhead box O; ROS, reactive oxygen species; AMPK, adenosine monophosphate activated protein kinase; COX-2, cyclooxygenase-2; MCP-1, monocyte chemoattractant protein-1; HIPK3, homeodomain-interacting protein kinase-3; HIF-1α, hypoxia inducible factor 1α; FN, fibronectin; GAS1, growth arrest-specific 1; ZEB1, zinc finger E-box binding homeobox 1; mTOR, mammalian target of rapamycin

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Currently, with the improvement of people's living standard and the changes in life style, the incidence of type 2 diabetes mellitus (T2DM) increased year by year. Diabetic kidney disease (DKD) is one of the most main microvascular complications of T2DM. And it is also one of the main reasons leading to end stage renal disease. More importantly, statistics data have shown that 20%-40% of people in patients with diabetes can develop DKD [1]. Consequently, early diagnosis and treatment of DKD could reduce or delay the onset of diabetic kidney damage, and improve the quality of patient's life. It will provide important clinical significance.

Recent study found that high glucose raises the expression of p53 in kidney. Inhibiting p53 expression attenuates high glucose-induced acute kidney injury [2]. Besides, p53 and microRNAs (miRNAs) may regulate transforming growth factor-β1 (TGF-β1) expression in diabetes mice to affect the development of diabetes renal fibrosis [3]. However, the role of p53 regulating miRNAs in DKD pathological mechanism is not yet clear. To clear the role of p53/miRNAs signaling in DKD mechanism may help to provide new train of thought for elucidating the pathological mechanism of DKD. In this paper we will review the role of p53/miRNAs signaling in DKD.

The function of p53

Transcription factor p53 plays an important role in the process of inhibiting tumor. It inhibits tumor formation by

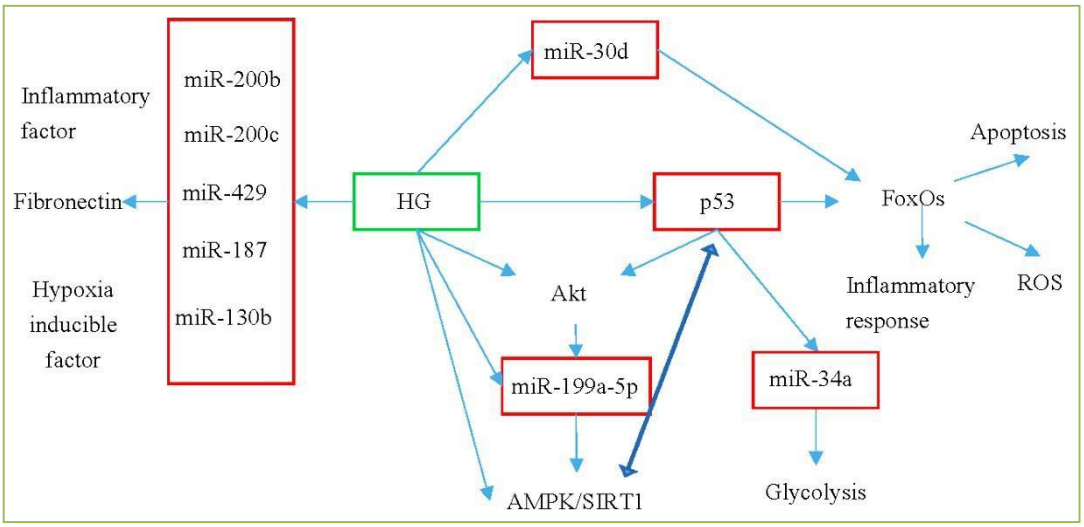

Figure 1. p53/miRNAs signaling related to diabetes development. HG: high glucose; Akt: serine/threonine kinase; AMPK: activating adenosine monophosphate activated protein kinase; SIRT1: sirtuin 1; FoxOs: forkhead box O; ROS: reactive oxygen species.

means of promoting DNA repair, preventing cell cycling, inducing cell aging and apoptosis [4, 5]. Sirtuin 1 (SIRT1) weakens the effect of p53 inhibiting tumor via deacetylation [6]. p53 activated by SIRT1 inhibitor increases the activity of nuclear factor κB p65 (NF-κB p65). Furthermore, it promotes cell apoptosis and the expression of pro-inflammatory factor as well [7]. SIRT1 may also suppress the activity of forkhead box O (FoxO) family via down-regulating p53 expression. And then it reduces reactive oxygen species (ROS) expression and apoptosis related to oxidative stress [8]. Activating adenosine monophosphate activated protein kinase (AMPK) phosphorylation can activate SIRT1, while suppressing AMPK activity can increase p53 acetylation [9]. It suggests that increasing the activity of AMPK phosphorylation may activate SIRT1 and attenuate the acetylation of p53, which results in inhibiting the activity of NF-κB p65 and FoxO. Thereby, AMPK/SIRT1 signaling inhibits cell apoptosis and decreases the expression of pro-inflammation factor via down-regulating p53.

Although p53 often acts as a protective factor in cancer, it is a pathogenic molecule in many non-cancer diseases. In islet β cell cytoplasm p53 induces mitochondria dysfunction and impaired insulin secretion. As a result, it promotes diabetes development [10]. Besides, high glucose increases p53 expression via inhibiting AMPK/SIRT1 signaling pathways in liver cells, which causes lipid accumulation and insulin resistance [11]. Further study used metformin to activate high glucose-inhibited AMPK/SIRT1 signaling pathway. And results revealed that the expression of p53 protein significantly decreased. While over-expressed p53 reduces the expression of SIRT1 protein and inhibits metformin-activated AMPK signaling, accompanied by the decrease of triglycerides [12]. It suggests that there is a bidirectional interaction between p53 and AMPK/SIRT1 signaling in the pathogenesis and treatment of diabetes. However, the specific mechanism of p53 in diabetes and its complications is not yet clear.

The function of microRNAs

As a kind of small non-encoded RNA in body, miRNAs can regulate target gene expression at the translation level, which depends on base pairing between the 'seed' area of miRNAs and the 3' untranslated regions of target genes' mRNAs [13]. Bioinformatics research found that miRNAs can adjust more than 60% gene expression in body [14]. miRNAs play an important role in cell growth, differentiation, apoptosis, and metabolism process. In addition, miRNAs are also involved in the pathogenesis of many diseases, such as oxidative stress, cardiovascular, cancer, and diabetes [15,16].

The expression of miR-200b, miR-429, and miR-200c increase significantly in diabetic vascular smooth muscle cells. And these miRNAs raise the expression of cyclooxygenase-2 (COX-2) and monocyte chemoattractant protein-1 (MCP-1), resulting in promoting inflammation [17]. miR-187 can decrease the expression of homeodomain-interacting protein kinase-3 (HIPK3), a factor regulating insulin secretion, and then reduce persistent hyperglycemia caused by glucose-stimulated insulin secretion [18]. Besides, high glucose promotes foxO3a expression via raising miR-30d expression, which raises the expression of inflammatory molecules and promotes cell apoptosis [19]. Research on diabetes patients also found that, with an increased level of urinary albumin, serum miR-130b level was significantly decreased and significantly negatively correlated with the serum levels of TGF-β1, hypoxia inducible factor 1α

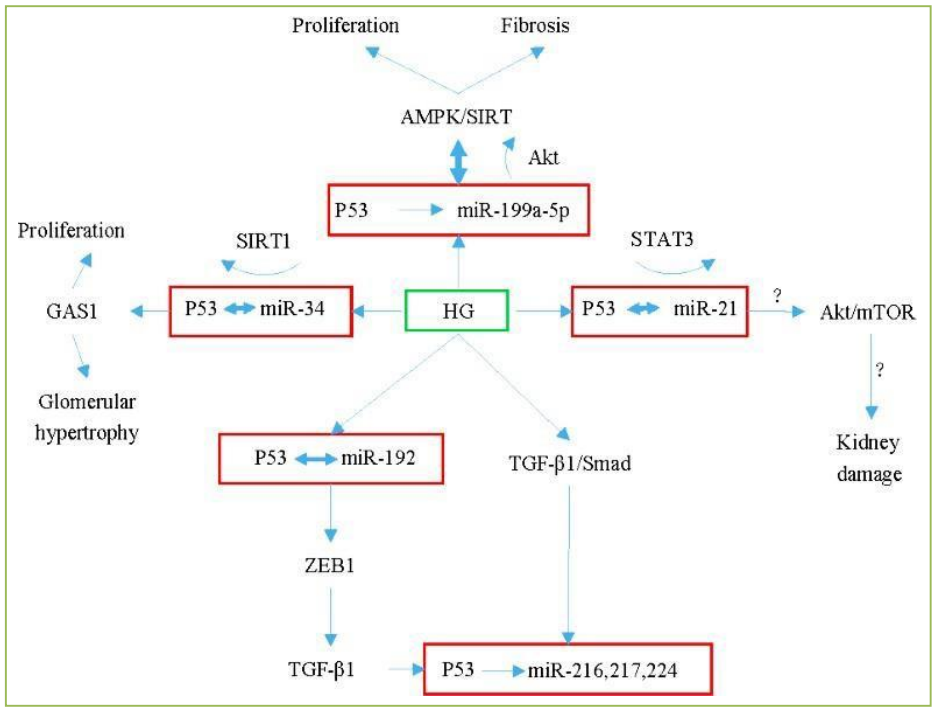

Figure 2. p53/miRNAs signaling related to diabetic kidney disease development. GAS1: growth arrest-specific 1; SIRT1: sirtuin 1; AMPK: activating adenosine monophosphate activated protein kinase; Akt: serine/threonine kinase; HG: high glucose; ZEB1: zinc finger E-box binding homeobox 1; TGF-β1: transforming growth factor-β1; STAT3: transcription 3; mTOR: mammalian target of rapamycin.

(HIF-1α), and fibronectin (FN) [20]. It prompts that miRNAs may influence the development of diabetes via adjusting multiple signaling mechanisms. Furthermore, it may play a role in DKD pathogenesis.

p53/microRNAs and diabetes

Although more and more evidences suggests that miRNAs play a regulatory role in metabolic disease, the mechanism of p53 participating in the process of miRNAs regulating metabolism is not clear yet [18,19].

p53 can inhibit glycolysis by regulating miR-34, and then adjust the activity of a series of glycolytic enzymes such as hexokinase 1, hexokinase 2, and glucose 6 phosphate isomerase to enhance mitochondrial respiration [21]. Cristhianna *et al*. [22] found that miR-199a-5p level has certain connection with diabetes development. Serine/threonine kinase (Akt) reduces miR-199a-5p expression, accompanied by higher SIRT1 expression. And overexpression of miR-199a-5p can reverse the change of SIRT1 expression [23]. What's more, studies found that p53 not only regulates the activity of Akt signaling pathways [24], also regulates AMPK/SIRT1 signaling pathways involved in the pathogenesis of diabetes mellitus [11,12]. It suggests that p53 may participate in the process of miRNAs regulating diabetes pathogenesis. It is important to further explore the mechanism of p53/miRNAs in the development of diabetes and its complications. (Fig. 1)

p53/microRNA and diabetic kidney disease

The early change of diabetic kidney damage is glomerular hemodynamics change, including high filtration and high perfusion damage [25]. And the main pathological features of DKD are glomerular basement membrane thickening, extracellular matrix accumulation [26], and interstitial inflammation [27]. It promotes the process of kidney structure damage, such as glomerular sclerosis and interstitial fibrosis, which eventually leads to kidney failure. p53/miRNAs signaling may adjust a variety of signaling pathways to regulate DKD development. But the mechanism has not been fully elucidated.

The role of p53/miR-34 signaling in DKD

p53 regulates cell apoptosis via inhibiting miR-34 expression [28]. Meanwhile, miR-34a can activate p53 to promote cell apoptosis by inhibiting SIRT1 expression [29]. In energy metabolism, p53 regulates miR-34 expression to inhibit glycolysis, and then enhances mitochondrial respiration [21]. Recent study has found that down-regulating miR-34 inhibits cell proliferation via inhibiting growth arrest-specific 1 (GAS1) in glomerular mesangial cells

cultured with high glucose. What's more, down-regulating miR-34 can alleviate glomerular hypertrophy in diabetes mice [30]. It suggests that p53 may play a role in the process of diabetic kidney damage via regulating miR-34 expression. (Fig. 2)

The role of p53/miR-192 signaling in DKD

The expression of miR-192 increases in patients with early DKD [31]. Furthermore, specifically inhibiting renal miR-192 expression alleviates renal fibrosis [32]. More importantly, study found that there is an interaction between p53 and miR-192, which regulates the downstream zinc finger E-box binding homeobox 1 (ZEB1) and TGF-β1 expression in diabetes mice renal. As a result, it affects the development of diabetic renal fibrosis [3]. It suggests that p53 may participate in the process of diabetic renal fibrosis through the mutual adjustment with miR-192, resulting in affecting the pathological development of DKD. (Fig. 2)

The role of p53/miR-199a and AMPK/SIRT1 signaling in DKD

High glucose raised p53 expression via inhibiting AMPK/SIRT1 signaling pathways [11]. Further evidence using metformin to activate AMPK/SIRT1 signaling can reduce p53 expression, while over-expressed p53 reduces the expression of SIRT1 [12]. Activating the phosphorylation of AMPK suppresses insulin resistance [33]. It also alleviates the activity of high glucose-stimulated mammalian target of rapamycin (mTOR)/p70S6K signaling pathways in glomerular mesangial cells, and thereby inhibits the expression of cell proliferation and fibrosis [34].

Besides, high glucose increases miR-199a-5p expression in glomerular mesangial cells [35]. Meanwhile, Akt reduces miR-199a-5p expression and raises SIRT1 expression. And over-expressed miR-199a-5p revises the expression of SIRT1 [23]. The ectopic expression of p53 induces miR-199a-3p transcription, and then affecting the restructuring of mice embryonic fibroblast cells [36]. We speculate that p53 may regulate DKD development by AMPK/SIRT1 signaling pathways, in which process miR-199a may play a certain role. (Fig. 2)

The role of p53/miR-21 and Akt/mTOR signaling in DKD

miR-21 negatively regulates the expression of p53 [37]. And p53 also influents miR-21 expression via regulating signaling transduction and signal transducer and activator of transcription 3 (STAT3) [38]. miR-21 expression appears significant change in early DKD [39]. Besides, miR-21 participates in diabetes related PI3K/Akt signaling and mTOR signaling [40]. However, its function and mechanism is still controversial. Zhao H *et al*. [41] considered that miR-21 regulates the activity of PI3K/Akt signaling to block glomerular stromal mast, which provides protection for early DKD [41]. Dey N *et al*. [41] considered that miR-21 may promote high glucose-induced mTOR expression and resulted in diabetic kidney damage. Research has found that activating p53 inhibits mTOR signaling [42]. Conversely, knocking out p53 gene significantly raises mTOR level and activates Akt protein [43]. More importantly, activating Akt/mTOR signaling increases DNA oxidative stress, and then promotes diabetic kidney damage [44]. It suggests that p53/miR-21 may participate in DKD development via regulating Akt/mTOR signaling. Further clarifying the mechanism is very important for clearing the pathogenesis of DKD. (Fig. 2)

The role of p53/miRNAs and TGF-β/Smad signaling in DKD

High glucose activates TGF-β/Smad signaling pathways to induce kidney ECM accumulating, which promotes interstitial fibrosis and glomerular mesangial expansion [25, 26]. There is a certain contact between miR-216, miR-217 and chronic kidney disease development. TGF-β up-regulates the expression of miR-216, 217 and activates Akt, resulting in contributing DKD development [45]. Kato M *et al*. [46] found that miR-192 could up-regulate these miRNAs expression. And p53 involved in the process of that miR-192 plays a role in the occurrence and development of DKD [3].

In addition, miR-224 not only plays a certain role in the development of diabetes, also plays a certain role in renal clear cell carcinoma [47]. More importantly, miR-224 participates in the process that TGF-β signaling pathways inhibits Smad4 expression. And p53 could inhibit miR-224 expression by combining the promoter of miR-224 coding gene. Conversely, down-regulating miR-224 expression activates p53 and inhibits Smad4 expression [48]. Therefore, we speculate p53/miRNAs may regulate the activity of TGF-β/Smad signaling to affect DKD development. (Fig. 2)

Based on the foregoing analysis, p53 and miRNAs has some correlation with DKD development. p53/miRNAs signaling may participate in a variety of signaling pathways regulating the pathological of DKD. However, the role of p53/miRNAs signaling in the pathological mechanism of DKD is not yet clear. To illuminate the role of p53/miRNAs signaling may inspire a new thinking for elucidating the pathological mechanism of DKD, and provide a new theoretical basis for the prevention and treatment of DKD.

Conflicting interests

The authors have declared that no competing interests exist.

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References

1. American Diabetes association. Standards of medical care in diabetes-2011. Diabetes Care 2011; 34:S11-S61.
2. Jianping P, Xiaoning L, Dongshan Z, Jian-Kang C, Yunchao S, Sylvia BS, *et al*. Hyperglycemia, p53 and mitochondrial pathway of apoptosis are involved in the susceptibility of diabetic models to ischemic acute kidney injury. Kidney Int 2015; 87:137-150.
3. Supriya DD, Sumanth P, Mei W, Jennifer YL, Markus B, Robert GN, *et al*. Transforming Growth Factor-b-Induced Cross Talk Between p53 and a MicroRNA in the Pathogenesis of Diabetic Nephropathy. Diabetes 2013; 62:3151-3162.
4. Junttila MR, Evan GI. p53-a Jack of all trades but master of none. Nat Rev Cancer 2009; 9:821-829.
5. Vousden KH, Prives C. Blinded by the light: The growing complexity of p53. Cell 2009; 137:413-431.
6. Homayoun V, Scott KD, Elinor NE, Shin-lchiro I, Roy AF, Tej KP, *et al*. hSIR2SIRT1 functions as an NAD-dependent p53 deacetylase. Cell 2001; 107:149-159.
7. Shohei S, Kyungho C, Michihiro S, Nobuyuki S, Marina Y, Tomokazu T, *et al*. Inflammatory stimuli induce inhibitory S-nitrosylation of the deacetylase SIRT1 to increase acetylation and activation of p53 and p65. Sci Signal 2014; 7:ra106.
8. Yusuke SH, Atsushi K, Ryusuke H, Yoshiyuki H. Regulation of FOXOs and p53 by SIRT1 Modulators under Oxidative Stress. PLoS One 2013; 8:e73875.
9. Alan WL, Pengda L, Hiroyuki I, Daming G. SIRT1 phosphorylation by AMP-activated protein kinase regulates p53 acetylation. Am J Cancer Res 2014; 4:245-255.
10. Atsushi H, Makoto A, Yoshifumi O, Satoshi K, Motoki U, Kuniyoshi F, *et al*. Inhibition of p53 preserves Parkin-mediated mitophagy and pancreatic β-cell function in diabetes. Proc Natl Acad Sci U S A 2014; 111:3116-3121.
11. Suchankova G, Nelson LE, Gerhart-Hines Z, Meghan K, Marie-Soleil G, Asish KS, *et al*. Concurrent regulation of AMP-activated protein kinase and SIRT1 in mammalian cells. Biochem Biophys Res Commun 2009; 378:836-841.
12. Lauren EN, Rudy JV, Jos éMC, Marie -Soleil G, Yasuo I, Neil BR. A novel inverse relationship between metformin-triggered AMPK-SIRT1 signaling and p53 protein abundance in high glucose-exposed HepG2 cells. Am J Physiol Cell Physiol 2012; 303:C4-C13.
13. Berezikov E. Evolution of microRNA diversity and regulation in animals. Nat Rev Genet 2011; 12:846-860.
14. Lewis BP, Burge CB, Bartel DP. Conserved seed pairing, often flanked by adenosines, indicates that thousands of human genes are microRNA targets. Cell 2005; 120:15-20.
15. Anna Z, Stefan K, Ignat D, Peter W, Ursula M, Marianna P. Plasma microRNA profiling reveals loss of endothelial miR-126 and other microRNAs in type 2 diabetes. Circ Res 2010; 107:810-817.
16. Munish K, Zhongxin L, Apana ALT, Weiqun C, Natalie SC, Kenneth SR, *et al*. Negative regulation of the tumor suppressor p53 gene by microRNAs. Oncogene 2011; 30:843-853.
17. Marpadga AR, Wen J, Louisa V, Mei W, Linda L, Ivan T, *et al*. Pro-Inflammatory Role of microRNA-200 in Vascular Smooth Muscle Cells from Diabetic Mice. Arterioscler Thromb Vasc Biol 2012; 32:721-729.
18. Locke JM, Xavier GS, D HR, Rutter GA, Harries LW. Increased expression of miR-187 in human islets from individuals with type 2 diabetes is associated with reduced glucose-stimulated insulin secretion. Diabetologia 2014; 57:122-128.
19. Li X, Du N, Zhang Q, Li J, Chen X, Liu X, *et al*. MicroRNA-30d regulates cardiomyocyte pyroptosis by directly targeting foxo3a in diabetic cardiomyopathy. Cell Death Dis 2014; 5:e1479.
20. Lv C, Zhou YH, Wu C, Shao Y, Lu CL, Wang QY. The changes in miR-130b levels in human serum and the correlation with the severity of diabetic nephropathy. Diabetes Metab Res Rev 2015; 31:717-724.
21. Kim HR, Roe JS, Lee JE, Cho EJ, Youn HD. p53 regulates glucose metabolism by miR-34a. Biochem Biophys Res Commun 2013; 437:225-231.
22. Collares CV, Evangelista AF, Xavier DJ, Rassi DM, Arns T, Foss-Freitas MC, *et al*. Identifying common and specific microRNAs expressed in peripheral blood mononuclear cell of type 1, type 2, and gestational diabetes mellitus patients. BMC Res Notes 2013; 6:491.
23. Rane S, He M, Sayed D, Yan L, Vatner D, Abdellatif M. An antagonism between the AKT and beta-adrenergic signaling pathways mediated through their reciprocal effects on miR-199a-5p. Cell Signal 2010; 22:1054-1062.
24. Manf è V, Biskup E, Rosbjerg A, Kamstru p M, Skov AG, Lerche CM, *et al*. miR-122 Regulates p53/Akt Signalling and the Chemotherapy-Induced Apoptosis in Cutaneous T-Cell Lymphoma. PLoS One 2012; 7:e29541.
25. Hostetter TH. Hyperfiltration and glomerulosclerosis. Semin Nephrol 2003; 23:194-199.
26. Ziyadeh EF: The extracellular matrix in diabetic nephropathy. Am J Kidney Dis 1993; 22:736-744,
27. Wang QY, Guan QH, Chen FQ. The changes of platelet-derived growth factor-BB (PDGF-BB) in T2DM and its clinical significance for early diagnosis of diabetic nephropathy. Diabetes Res Clin Pract. 2009; 85:166-170.
28. He L, He X, Lim LP, Stanchina E, Xuan Z, Liang Y, *et al*. A microRNA component of the p53 tumour suppressor network. Nature 2007; 447,1130-1134.
29. Yamakuchi M, Ferlito M, Lowenstein CJ. miR-34 a repression of SIRT1 regulates apoptosis. Proc Natl Acad Sci U S A 2008; 105:13421-13426.
30. Zhang L, He S, Guo S, Xie W, Xin R, Yu H, *et al*. Down-regulation of miR-34a alleviates mesangial proliferation in vitro and glomerular hypertrophy in early diabetic nephropathy mice by targeting GAS1. J Diabetes Complications 2014;

28:259-264.

31. Krupa A, Jenkins R, Luo DD, Lewis A, Phillips A, Fraser D. Loss of MicroRNA-192 Promotes Fibrogenesis in Diabetic Nephropathy. J Am Soc Nephrol 2010; 21:438-447.
32. Putta S, Lanting L, Sun G, Lawson G, Kato M, Natarajan R. Inhibiting microRNA-192 ameliorates renal fibrosis in diabetic nephropathy. J Am Soc Nephrol 2012; 23:458-469.
33. Saha AK, Xu XJ, Lawson E, Deoliveira R, Brandon AE, Kraegen EW, *et al*. Down regulation of AMPK Accompanies Leucine- and Glucose-Induced Increases in Protein Synthesis and Insulin Resistance in Rat Skeletal Muscle. Diabetes 2010, 59:2426-2434.
34. Lv C, Wu C, Zhou YH, Shao Y, Wang G, Wang QY. Alpha Lipoic Acid Modulated High Glucose-Induced Rat Mesangial Cell Dysfunction via mTOR/p70S6K/4E-BP1 Pathway. Int J Endocrinol 2014; 2014:658589.
35. Wu C, Lv C, Chen FQ, Ma XY, Shao Y, Wang QY. The function of miR-199a-5p/Klotho regulating TLR4/NF-k B p65/NGAL pathways in rat mesangial cells cultured with high glucose and the mechanism. Mol Cell Endocrinol 2015; 417:84-93.
36. Wang J, He Q, Han C, *et al*. p53-facilitated miR-199a-3p regulates somatic cell reprogramming. Stem Cells 2012; 30:1405-1413.
37. Papagiannakopoulos T, Shapiro A, Kosik KS. MicroRNA-21 targets a network of key tumor-suppressive pathways in glioblastoma cells. Cancer Res 2008; 68:8164-8172.
38. Choy MK, Movassagh M, Siggens L, Vujic A, Goddard M, Sanchez A, *et al*. Research High-throughput sequencing identifies STAT3 as the DNA-associated factor for p53-NF-κB-complex-dependent gene expression in human heart failure. Genome Med 2010; 2:37.
39. Dey N, Das F, Mariappan MM, Mandal CC, Ghosh-Choudhury N, Kasinath BS, *et al*. MicroRNA-21 orchestrates high glucose-induced signals to TOR complex 1, resulting in renal cell pathology in diabetes. J Biol Chem 2011; 286:25586-25603.
40. Zhao H, Yang J, Fan T, Li S, Ren X. RhoE functions as a tumor suppressor in esophageal squamous cell carcinoma and modulates the PTEN/PI3K/Akt signaling pathway. Tumour Biol 2012; 33:1363-1374.
41. Chow TF, Youssef YM, Lianidou E, Romaschin AD, Honey RJ, Stewart R, *et al*. Differential expression profiling of microRNAs and their potential involvement in renal cell carcinoma pathogenesis. Clin Biochem 2010; 43:150-158.
42. Demidenko ZN, Korotchkina LG, Gudkov AV, Blagosklonny MV. Paradoxical suppression of cellular senescence by p53. Proc Natl Acad Sci U S A 2010; 107:9660-9664.
43. Leontieva OV, Novototskaya LR, Paszkiewicz GM, Komarova EA, Gudkov AV, Blagosklonny MV. Dysregulation of the mTOR pathway in p53-deficient mice. Cancer Biol Ther 2013; 14:1182-1188.
44. Habib SL, Liang S. Hyperactivation of Akt/mTOR and deficiency in tuberin increased the oxidative DNA damage in kidney cancer patients with diabetes. Oncotarget 2014; 5:2542-2550.
45. Li JY, Yong TY, Michael MZ, Gleadle JM. Review: The role of microRNAs in kidney disease. Nephrology (Carlton) 2010; 15:599-608.
46. Kato M, Putta S, Wang M, Yuan H, Lanting L, Nair I, *et al*. TGF-beta activates Akt kinase through a microRNA-dependent amplifying circuit targeting PTEN. Nat Cell Biol 2009; 11:881-889.
47. Boguslawska J, Wojcicka A, Piekielko-Witkowska A, Master A, Nauman A. MiR-224 Targets the 3′UTR of Type 1 5′-Iodothyronine Deiodinase Possibly Contributing to Tissue Hypothyroidism in Renal Cancer. PLoS One 2011; 6: e24541.
48. Liang M, Yao G, Yin M, Lv M, Tian H, Liu L, *et al*. Transcriptional cooperation between p53 and NF-kappaB p65regulates microRNA-224 transcription in mouse ovarian granulosa cells. Mol Cell Endocrinol 2013; 370:119-129.