Biochemical and Biophysical Research Communications 425 (2012) 741–745

Contents lists available at SciVerse ScienceDirect

Biochemical and Biophysical Research Communications

journal homepage: www.elsevier.com/locate/ybbrc

Genetic analysis of the SIRT1 gene promoter in ventricular septal defects

Jiping Shan [a,1], Shuchao Pang [a,1], Hongxin Wanyan [a,1], Wen Xie [b], Xianyun Qin [a], Bo Yan [a,c,*]

[a] Shandong Provincial Key Laboratory of Cardiac Disease Diagnosis and Treatment, Jining Medical University Affiliated Hospital, Jining Medical University, Jining, Shandong 272029, PR China
[b] Division of Ultrasound Medicine, Jining Medical University Affiliated Hospital, Jining Medical University, Jining, Shandong 272029, PR China
[c] Sino-US Joint Laboratory of Translational Medicine, Jining Medical University Affiliated Hospital, Jining Medical University, Jining, Shandong 272029, PR China

ARTICLE INFO

Article history:
Received 17 July 2012
Available online 3 August 2012

Keywords:
Congenital heart disease
Ventricular septal defects
SIRT1
Promoter
Sequence variants

ABSTRACT

Mutations in cardiac transcription factor genes, such as GATA-4, NKX2-5 and TBX5 genes, have been associated to the patients with familial and isolated congenital heart disease (CHD). Little work has been done on the epigenetic causes for CHD. Sirtuis are highly conserved NAD-dependent class III deacetylases. In mammals, there are seven members of surtuin family, SIRT1–SIRT7. SIRT1, the closest to yeast Sir2, has deacetylase activity and ADP-ribosyltransferase activity. SIRT1 has been involved in many cellular processes and implicated in human diseases, such as obesity, type 2 diabetes, cancer and neurodegenerative diseases. We hypothesized that altered levels of SIRT1 gene expression, rather than mutations in SIRT1 gene, may contribute to the human diseases. In this study, we genetically analyze the SIRT1 gene promoter in patients with ventricular septal defects (VSD) (n = 333) and ethic-matched healthy controls (n = 348). In all, six single-nucleotide polymorphisms (SNPs) and twelve heterozygous sequence variants were identified. Four novel heterozygous variants, g.69643693A > G, g.69643963A > T, g.69643971G > A and g.69644366Ins, were found in six VSD patients, but in none of controls. Six SNPs and variants, g.69643707A > C (rs35706870), g.69643874C > A, g.69644209C > G, g.69644213G > A, g.69644268T > A and g.69644441G > A, were only identified in controls. The other SNPs and variants were found in both groups with similar frequencies. Therefore, the variants within the SIRT1 gene promoter identified in VSD patients may alter the transcriptional activities of SIRT1 gene promoter. Changed SIRT1 protein levels may contribute to the VSD etiology by affecting the activities of its substrates.

1. Introduction

Congenital heart disease (CHD) is the most common type of birth defects in humans, with the prevalence of 4–50 per 1000 live births [1]. Epidemiological studies have shown that morbidity and mortality in CHD patients are significantly higher than general population, even after effective surgical correction [2,3]. The main death causes are late cardiac complications, including arrhythmias, coronary heart disease and heart failure, which are probably due to genetic defects. However, the genetic causes and underlying molecular mechanisms for CHD remain largely unknown.

During the embryonic development, the heart is the first organ to form. The progenitor cells originating from the first heart field, second heart field and cardiac neural crest contribute to the cardiac morphogenesis [4,5]. The heart development is strictly regulated by a cardiac regulatory gene network involving signaling pathways and cardiac transcription factors [6,7]. To date, mutations in cardiac transcription factor genes, such as GATA transcription factor 4 (GATA4), T-box transcription factor 5 (TBX5) and NK2 transcription factor, locus 2 (NKX2-5), have been associated to a small portion of CHD cases [8]. GATA4, TBX5, NKX2-5 and other factors have been shown to function in a dosage-dependent manner [9–11]. We have previously analyzed the promoter regions of GATA4, NKX2-5, TBX5 and TBX20 genes, and identified a number of the sequence variants that are linked to VSD [12–15]. To date, epigenetic studies in CHD patients have not been reported.

Sirtuins, NAD-dependent class III deacetylases, are highly conserved from yeast to human [16]. Surtuins have been shown to expand lifespan in yeast, worm and fly. Seven members of sirtuin family, SIRT1–SIRT7, have been identified in mammals. SIRT1, the founding member and the closest to yeast Sir2, is localized in the nucleus and the cytoplasm and has deacetylase and ADP-ribosyltransferase activities. In epigenetic regulation, SIRT1 plays an essential role by deacetylating histones. Moreover, SIRT1 interacts and deacetylates a broad set of transcription factors and regulators to control downstream gene expression. Physiologically, SIRT1 has been involved in cell survival and differentiation, genomic stability, tran-

* Corresponding author. Address: Shandong Provincial Key Laboratory of Cardiac Disease Diagnosis and Treatment, Jining Medical University Affiliated Hospital, Jining Medical University, 79 Guhuai Road, Jining, Shandong 272029, PR China. Fax: +86 0537 2213030.
E-mail addresses: yanbo@mail.jnmc.edu.cn, jnmcyan@gmail.com (B. Yan).
[1] These authors contributed equally to the work.

0006-291X/$ - see front matter © 2012 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.bbrc.2012.07.145

Table 1
Sequence variants within the SIRT1 gene promoters in VSD patients and controls.

Sequence variants	Genotypes	Location[a]	VSD (n = 333)	Controls (n = 348)	P value
g.69643693A > G	AG	−834 bp	1	0	–
g.69643707A > C (rs35706870)	AC	−820 bp	0	1	–
g.69643759A > T	AT	−768 bp	1	2	1.000
g.69643874C > A	CA	−553 bp	0	1	–
g.69643959A > G (rs3740051)	AA	−468 bp	200	177	0.052
	AG		117	149	
	GG		16	22	
g.69643963A > T	AT	−464 bp	1	0	–
g.69643971G > A	GA	−456 bp	3	0	–
g.69644209C > G	CG	−218 bp	0	1	–
g.69644213G > A	GA	−214 bp	0	2	–
g.69644217A > C (rs932658)	AA	−210 bp	229	226	0.560
	AC		97	113	
	CC		7	9	
g.69644219G > A	GA	−208 bp	1	4	0.201
g.69644240G > T (rs35995735)	GG	−187 bp	322	337	0.916
	GT		11	11	
	TT		0	0	
g.69644268T > A	TA	−159 bp	0	1	–
g.69644335A > G (rs3740053)	AA	−92 bp	192	171	0.083
	AG		122	152	
	GG		19	25	
g.69644341G > C (rs2394443)	GG	−86 bp	230	226	0.481
	GC		96	112	
	CC		7	10	
g.69644351G > A	GA	−76 bp	1	1	1.000
g.69644366Ins	−/17 bp	−74 bp	1	0	–
g.69644441G > A	GA	+15	0	1	–

[a] Locations of variants upstream (−) or downstream (+) to the transcription start site at 69644427 of NC_000010.10.

scription, metabolism, stress response and aging. Clinically, SIRT1 has been implicated in inflammation, obesity, type 2 diabetes, cardiovascular diseases, neurodegenerative diseases and cancer [17–20].

Studies in experimental animals have demonstrated that SIRT1 is essential to the embryonic development. Most of mice with SIRT1 null deletion died perinatally with cardiac defects, including atrial septal, ventricular septal, and heart valve defects [21–23]. In mouse embryos, SIRT1 is predominantly expressed in the heart and brain [24]. In human, the expression level of SIRT1 is relatively high in the heart, brain and skeletal muscle tissues [25]. These studies suggest that SIRT1 plays a critical role in the cardiogenesis. Therefore, we hypothesized that altered SIRT1 gene expression levels, rather than changed amino acids of SIRT1 protein, may contribute to the CHD etiology. In this study, SIRT1 gene promoter was genetically analyzed in large cohorts of patients with ventricular septal defects (VSD) and healthy controls.

2. Materials and methods

2.1. Patients and controls

All VSD patients (n = 333, male 155, female 178, age range 3 month–41 years, median age 4.75 years) and healthy controls (n = 348, male 271, female 77, age range 1 month–34.00 years, median age 3.41 years) were recruited from Jining Medical University Affiliated Hospital, Jining Medical University, Jining, Shandong, China. The VSD patients were diagnosed with physical examination, electrocardiogram and three-dimensional echocardiography. The VSD patients and controls with familial histories were excluded from this study. This study was approved by the Human Ethic Committee of Jining Medical University Affiliated Hospital and informed consents were obtained from the patients and controls or the guardians.

2.2. Genetic analysis

Peripheral leukocytes were isolated and genomic DNAs were extracted with QIAGEN DNeasy Blood and Tissue Kit (Qiagen, Valencia, CA, USA). The SIRT1 gene promoter, −841 bp upstream to +237 bp downstream to the transcription start site, was analyzed. Two overlapped DNA fragments covering the SIRT1 gene promoter, −841 bp ∼ −321 bp (521 bp) and −355 bp ∼ +327 bp (592 bp), were generated by PCR with supermix (Invitrogen, Carlsbad, CA, USA). The genomic DNAs (100 ng) were used as PCR templates. The PCR primers were designed with the genomic sequence of human SIRT1 gene (Genebank access number, NG_000010). The PCR primers, SIRT1-F1 (5′-AGAGGAAAGTGGAAGGGCTT-3′) and SIRT1-R1 (5′-TTTCCCACTCTCCTCACACC-3′), were used to generate the 521 bp fragment. The primers, SIRT1-F2 (5′-AGGAGCTGTCAGAACGGTGT-3′) and SIRT1-R2 (5′-CCATCTTCCAACTGCCTCTC-3′), were used to generate the 592 bp fragment. The DNA fragments were sequenced on a 3730 DNA Analyzer (Applied Biosystems, Foster city, CA, USA). The sequences were aligned and compared with wild type SIRT1 gene promoter. The distributions of sequence variants were compared between VSD patients and controls using SPSS v13.0. $P < 0.05$ was considered statistically significant.

3. Results

The distribution of the sequence variants identified within SIRT1 gene promoter were summarized in Table 1. Total 18 single-nucleotide polymorphisms (SNPs) and sequence variants were identified in this study. Four novel heterozygous sequence variants, g.69643693A > G, g.69643963A > T, g.69643971G > A and g.69644366Ins, were identified in VSD patients, but in none of controls. In contrast, six SNPs and heterozygous variants, g.69643707A > C (rs35706870), g.69643874C > A, g.69644209C > G, g.69644213G > A, g.69644268T > A and g.69644441G > A, were only found in controls (Fig 1A and B). The other SNPs and variants, g.69643759A > T, g.69643959A > G (rs3740051), g.69644217A > C (rs932658), g.69644219G > A, g.69644240G > T (rs35995735), g.69644335A > G (rs3740053), g.69644341G > C (rs2394443) and g.69644351G > A, were found in VSD patients and controls with similar frequencies. The variant, g.69644213G > A, which has been previously reported in Parkinson's disease [26], was linked with

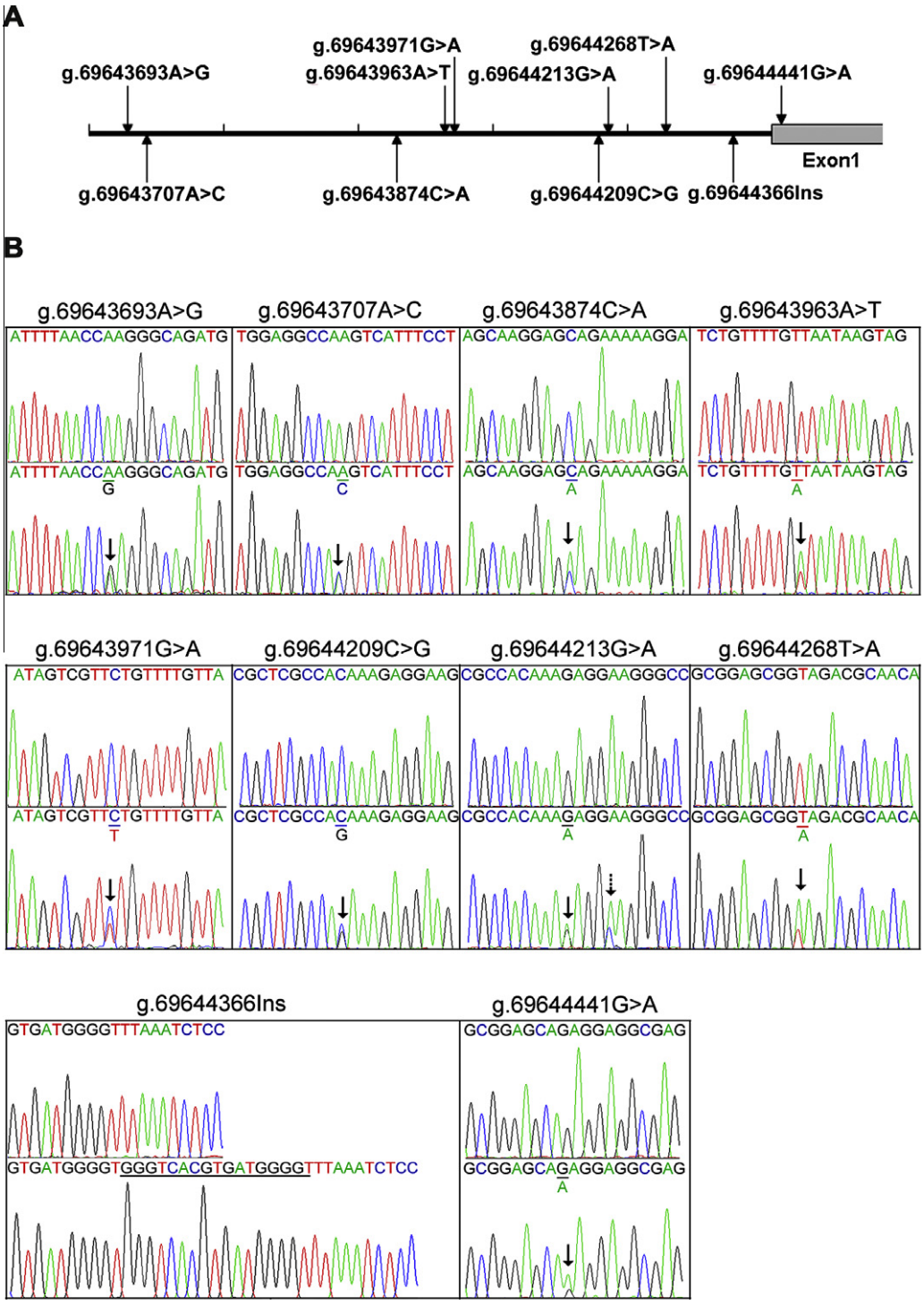

Fig. 1. The sequence variants within the SIRT1 gene promoter in VSD patients and controls. A. Schematic representation of the sequence variants within SIRT1 gene promoter. The sequence variants, which were of clinical importance, were depicted. The numbers represents the sequence of SIRT1 genomic sequences (Genebank accession number NC_000010). The transcription starts at the position of 69644427 of the first exon. B. Chromatograms of the heterozygous sequence variants. The variants, g.69643963A > T and g.69643971G > A, were in reverse orientation, the others were in forward orientation. Top panel shows wild type and bottom heterozygous. All the variants are marked with solid arrows. The SNP, g.69644217A > C (rs932658), which was linked with the variant g.69644213G > A, was indicated with dashed arrow. In the variant, g.69644366Ins, the 17 bp insertion was underlined.

g.69644217A > C (rs932658) and identified in two controls. Analysis of SIRT1 gene promoter region with transcription element search system (TESS, University of Pennsylvania) revealed that the novel variants identified in VSD patients may change transcription factor binding sites. Therefore, the transcriptional activity of the SIRT1 gene promoter may be altered by these sequence variants in VSD patients.

4. Discussion

The SNPs and variants in SIRT1 gene have been shown to increase the risk for obesity, type 2 diabetes and Parkinson's disease [26–29]. SIRT1 polymorphisms have been associated with abnormal cholesterol metabolism, body fat and coronary artery calcification [30,31]. In this study, we, for the first time, linked the

sequence variants within SIRT1 gene promoter with VSD patients. Four novel heterozygous sequence variants within the SIRT1 gene promoter, g.69643693A > G, g.69643963A > T, g.69643971G > A and g.69644366Ins, were identified in VSD patients, but in none of controls. Therefore, these variants may alter the transcriptional activities of SIRT1 gene promoter and change SIRT1 levels, contributing to the VSD etiology.

Human SIRT1 gene is localized to the chromosome region 10q21.3, containing 9 exons [32,33]. Although SIRT1 is widely expressed in fetal and adult tissues, the expression level of SIRT1 gene is relatively high in the heart [25]. SIRT1 gene expression is regulated by a set of transcriptional factors, including CREB (cAMP response element-binding protein), FOXO (forkhead box transcription factor O), HIC1 (hypermethylated in cancer 1), PARP-2 (poly (ADP-ribose) polymerase-2) and PPARs (peroxisome proliferator-activated receptors) [34–38]. We have previously reported the variants within the SIRT1 gene promoter in sporadic Parkinson's disease [26]. The results from this study will broaden the range of the SIRT1 association with human diseases.

Many non-histone substrates for SIRT1 have been identified, including P53, Forkhead box O (FOXO) transcription factors, MEF2 and PGC-1a [18–20,39–44]. Some of these substrates have been shown to play important roles in the heart development. For example, gene targeting studies in mice have demonstrated that FoxO1 is required for the initial formation of the cardiovascular system during development. Mice with genomic loss of FOXO1 died at embryonic day 10.5 with heart malformation [45,46]. Cardiac-specific expression of FoxO3 leads to reversible heart atrophy in transgenic mice [47]. Cardiac specific disruption of MEF2 activity inhibits cardiomyogenesis in mice [48]. In human, MEF2 gene is expressed in all developmental stage of the human heart [49]. Therefore, changed SIRT1 may interfere with the heart development through affecting the activities of these transcription factors.

Mutual regulation and interaction of SIRT1 and cardiac transcription factors, such as GATA4, TBX5 and NKX2-5, have not been reported. Recent studies indicate that the activities of cardiac transcription factors can be regulated by epigenetic modifying enzymes. For example, overexpression of SIRT3, another member of surtuin family, repressed GATA4 activity in transgenic mice [50]. T-box domain of TBX transcription factors can interact with epigenetic modifying enzymes to form complexes [51]. Polycomb-repressive complex 2 (PRC2) methylates GATA4 and inhibits its transcriptional activity [52]. Therefore, SIRT1 may regulate and interact with cardiac transcription factors in the heart development in the same manner. Changed SIRT1 may directly or indirectly affected activities of cardiac transcription factors.

In conclusion, we genetically analyzed the SIRT1 gene promoter in large cohorts of VSD patients and controls. The novel heterozygous variants identified in VSD patients may change SIRT1 protein levels, contributing to the VSD etiology by regulating transcription factors involved in the heart development. As natural and chemical compounds have been found to regulate SIRT1 activities [53], our findings may provide the basis for designing potential therapies for adult CHD patients.

Acknowledgments

This study was supported by National Natural Science Foundation of China (No. 81070173), Shandong Provincial Natural Science Foundation (ZR2010HL030 and ZR2010HL111).

References

[1] M.E. Pierpont, C.T. Basson, D.W. Benson Jr, et al., Genetic basis for congenital heart defects: current knowledge: a scientific statement from the American Heart Association Congenital Cardiac Defects Committee, Council on Cardiovascular Disease in the Young: endorsed by the American Academy of Pediatrics, Circulation 115 (2007) 3015–3038.
[2] T. van der Bom, A.C. Zomer, A.H. Zwinderman, F.J. Meijboom, B.J. Bouma, B.J. Mulder, The changing epidemiology of congenital heart disease, Nat. Rev. Cardiol. 8 (2011) 50–60.
[3] C.L. Verheugt, C.S. Uiterwaal, E.T. van der Velde, et al., Mortality in adult congenital heart disease, Eur. Heart J. 31 (2010) 1220–1229.
[4] M. Buckingham, S. Meilhac, S. Zaffran, Building the mammalian heart from two sources of myocardial cells, Nat. Rev. Genet. 6 (2005) 826–835.
[5] D. Srivastava, Making or breaking the heart: from lineage determination to morphogenesis, Cell 126 (2006) 1037–1048.
[6] S.L. Dunwoodie, Combinatorial signaling in the heart orchestrates cardiac induction, lineage specification and chamber formation, Semin. Cell Dev. Biol. 18 (2007) 54–66.
[7] F. Rochais, K. Mesbah, R.G. Kelly, Signaling pathways controlling second heart field development, Circ. Res. 104 (2009) 933–942.
[8] B.G. Bruneau, The developmental genetics of congenital heart disease, Nature 451 (2008) 943–948.
[9] P.Y. Jay, O. Rozhitskaya, O. Tarnavski, et al., Haploinsufficiency of the cardiac transcription factor Nkx2-5 variably affects the expression of putative target genes, FASEB J. 19 (2005) 1495–1497.
[10] A.V. Postma, J.B. van de Meerakker, I.B. Mathijssen, et al., A gain-of-function TBX5 mutation is associated with a typical Holt–Oram syndrome and paroxysmal a trial fibrillation, Circ. Res. 102 (2008) 1433–1442.
[11] W.T. Pu, T. Ishiwata, A.L. Juraszek, Q. Ma, S. Izumo, GATA4 is a dosage-sensitive regulator of cardiac morphogenesis, Dev. Biol. 275 (2004) 235–244.
[12] S. Pang, J. Shan, Y. Qiao, et al., Genetic and Functional Analysis of the NKX2-5 Gene Promoter in Patients with Ventricular Septal Defects, Pediatr. Cardiol, 2012, in press.
[13] Y. Qiao, H. Wanyan, Q. Xing, et al., Genetic analysis of the TBX20 gene promoter region in patients with ventricular septal defects, Gene 500 (2012) 28–31.
[14] J. Shan, S. Pang, Y. Qiao, et al., Functional analysis of the novel sequence variants within TBX5 gene promoter in patients with ventricular septal defects, Transl. Res, 2012, in press.
[15] G. Wu, J. Shan, S. Pang, X. Wei, H. Zhang, B. Yan, Genetic analysis of the promoter region of the GATA4 gene in patients with ventricular septal defects, Transl. Res. 159 (2012) 376–382.
[16] S. Imai, C.M. Armstrong, M. Kaeberlein, L. Guarente, Transcriptional silencing and longevity protein Sir2 is an NAD-dependent histone deacetylase, Nature 403 (2000) 795–800.
[17] T. Finkel, C.X. Deng, R. Mostoslavsky, Recent progress in the biology and physiology of sirtuins, Nature 460 (2009) 587–591.
[18] M.C. Haigis, D.A. Sinclair, Mammalian sirtuins: biological insights and disease relevance, Annu. Rev. Pathol. 5 (2010) 253–295.
[19] Y. Horio, T. Hayashi, A. Kuno, R. Kunimoto, Cellular and molecular effects of sirtuins in health and disease, Clin. Sci. (Lond) 121 (2011) 191–203.
[20] R.H. Houtkooper, E. Pirinen, J. Auwerx, Sirtuins as regulators of metabolism and healthspan, Nat. Rev. Mol. Cell Biol. 13 (2012) 225–238.
[21] C.P. Chang, B.G. Bruneau, Epigenetics and cardiovascular development, Annu. Rev. Physiol. 74 (2012) 41–68.
[22] H.L. Cheng, R. Mostoslavsky, S. Saito, et al., Developmental defects and p53 hyperacetylation in Sir2 homolog (SIRT1)-deficient mice, Proc. Natl. Acad. Sci. USA 100 (2003) 10794–10799.
[23] M.W. McBurney, X. Yang, K. Jardine, et al., The mammalian SIR2alpha protein has a role in embryogenesis and gametogenesis, Mol. Cell. Biol. 23 (2003) 38–54.
[24] J. Sakamoto, T. Miura, K. Shimamoto, Y. Horio, Predominant expression of Sir2alpha, an NAD-dependent histone deacetylase, in the embryonic mouse heart and brain, FEBS Lett. 556 (2004) 281–286.
[25] G. Afshar, J.P. Murnane, Characterization of a human gene with sequence homology to Saccharomyces cerevisiae SIR2, Gene 234 (1999) 161–168.
[26] A. Zhang, H. Wang, X. Qin, S. Pang, B. Yan, Genetic analysis of SIRT1 gene promoter in sporadic Parkinson's disease, Biochem. Biophys. Res. Commun. 422 (2012) 693–696.
[27] S.J. Clark, M. Falchi, B. Olsson, et al., Association of sirtuin 1 (SIRT1) gene SNPs and transcript expression levels with severe obesity, Obesity (Silver Spring) 20 (2012) 178–185.
[28] Y. Dong, T. Guo, M. Traurig, et al., SIRT1 is associated with a decrease in acute insulin secretion and a sex specific increase in risk for type 2 diabetes in Pima Indians, Mol. Genet. Metab. 104 (2011) 661–665.
[29] M.C. Zillikens, J.B. van Meurs, F. Rivadeneira, et al., SIRT1 genetic variation is related to BMI and risk of obesity, Diabetes 58 (2009) 2828–2834.
[30] Y. Shimoyama, K. Suzuki, N. Hamajima, T. Niwa, Sirtuin 1 gene polymorphisms are associated with body fat and blood pressure in Japanese, Transl. Res. 157 (2011) 339–347.
[31] Y. Shimoyama, Y. Mitsuda, Y. Tsuruta, K. Suzuki, N. Hamajima, T. Niwa, SIRTUIN 1 gene polymorphisms are associated with cholesterol metabolism and coronary artery calcification in Japanese hemodialysis patients, J. Ren. Nutr. 22 (2012) 114–119.
[32] R.A. Frye, Characterization of five human cDNAs with homology to the yeast SIR2 gene: Sir2-like proteins (sirtuins) metabolize NAD and may have protein ADP-ribosyltransferase activity, Biochem. Biophys. Res. Commun. 260 (1999) 273–279.

[33] S. Voelter-Mahlknecht, U. Mahlknecht, Cloning, chromosomal characterization and mapping of the NAD-dependent histone deacetylases gene sirtuin 1, Int. J. Mol. Med. 17 (2006) 59–67.
[34] P. Bai, C. Canto, A. Brunyánszki, et al., PARP-2 regulates SIRT1 expression and whole-body energy expenditure, Cell Metab. 13 (2011) 450–460.
[35] W.Y. Chen, D.H. Wang, R.C. Yen, J. Luo, W. Gu, S.B. Baylin, Tumor suppressor HIC1 directly regulates SIRT1 to modulate p53-dependent DNA-damage responses, Cell 123 (2005) 437–448.
[36] L. Han, R. Zhou, J. Niu, M.A. McNutt, P. Wang, T. Tong, SIRT1 is regulated by a PPAR{γ}-SIRT1 negative feedback loop associated with senescence, Nucleic Acids Res. 38 (2010) 7458–7471.
[37] S. Nemoto, M.M. Fergusson, T. Finkel, Nutrient availability regulates SIRT1 through a forkhead-dependent pathway, Science 306 (2004) 2105–2108.
[38] L.G. Noriega, J.N. Feige, C. Canto, et al., CREB and ChREBP oppositely regulate SIRT1 expression in response to energy availability, EMBO Rep. 12 (2011) 1069–1076.
[39] A. Brunet, L.B. Sweeney, J.F. Sturgill, et al., Stress-dependent regulation of FOXO transcription factors by the SIRT1 deacetylase, Science 303 (2004) 2011–2015.
[40] J. Luo, A.Y. Nikolaev, S. Imai, et al., Negative control of p53 by Sir2alpha promotes cell survival under stress, Cell 107 (2001) 137–148.
[41] M.C. Motta, N. Divecha, M. Lemieux, et al., Mammalian SIRT1 represses forkhead transcription factors, Cell 116 (2004) 551–563.
[42] J.T. Rodgers, C. Lerin, W. Haas, S.P. Gygi, B.M. Spiegelman, P. Puigserver, Nutrient control of glucose homeostasis through a complex of PGC-1alpha and SIRT1, Nature 434 (2005) 113–118.
[43] H. Vaziri, S.K. Dessain, E. Ng Eaton, et al., HSIR2(SIRT1) functions as an NAD-dependent p53 deacetylase, Cell 107 (2001) 149–159.
[44] X. Zhao, T. Sternsdorf, T.A. Bolger, R.M. Evans, T.P. Yao, Regulation of MEF2 by histone deacetylase 4- and SIRT1 deacetylase-mediated lysine modifications, Mol. Cell. Biol. 25 (2005) 8456–8464.
[45] T. Furuyama, K. Kitayama, Y. Shimoda, et al., Abnormal angiogenesis in Foxo1 (Fkhr)-deficient mice, J. Biol. Chem. 279 (2004) 34741–34749.
[46] T. Hosaka, W.H. Biggs 3rd, D. Tieu, et al., Disruption of forkhead transcription factor (FOXO) family members in mice reveals their functional diversification, Proc. Natl. Acad. Sci. USA 101 (2004) 2975–2980.
[47] T.G. Schips, A. Wietelmann, K. Höhn, et al., FoxO3 induces reversible cardiac atrophy and autophagy in a transgenic mouse model, Cardiovasc. Res. 91 (2011) 587–597.
[48] K. Iida, K. Hidaka, M. Takeuchi, et al., Expression of MEF2 genes during human cardiac development, Tohoku J. Exp. Med. 187 (1999) 15–23.
[49] C. Karamboulas, G.D. Dakubo, J. Liu, et al., Disruption of MEF2 activity in cardiomyoblasts inhibits cardiomyogenesis, J. Cell Sci. 119 (2006) 4315–4321.
[50] N.R. Sundaresan, M. Gupta, G. Kim, S.B. Rajamohan, A. Isbatan, M.P. Gupta, Sirt3 blocks the cardiac hypertrophic response by augmenting Foxo3a-dependent antioxidant defense mechanisms in mice, J. Clin. Invest. 119 (2009) 2758–2771.
[51] S.A. Miller, A.C. Huang, M.M. Miazgowicz, M.M. Brassil, A.S. Weinmann, Coordinated but physically separable interaction with H3K27-demethylase and H3K4-methyltransferase activities are required for T-box protein-mediated activation of developmental gene expression, Genes Dev. 22 (2008) 2980–2993.
[52] A. He, X. Shen, Q. Ma, et al., PRC2 directly methylates GATA4 and represses its transcriptional activity, Genes Dev. 26 (2012) 37–42.
[53] S. Lavu, O. Boss, P.J. Elliott, P.D. Lambert, Sirtuins–novel therapeutic targets to treat age-associated diseases, Nat. Rev. Drug Discovery 7 (2008) 841–853.