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Genetic analysis of the SIRT1 gene promoter in myocardial infarction

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ABSTRACT

Myocardial infarction (MI) is a restrictive phenotype of coronary artery disease. To date, a group of genes and genetic loci have been associated to MI. However, the genetic causes and underlying molecular mechanisms for MI remain largely unknown. SIRT1, one of highly conserved NAD-dependent class III deacetylases, has been involved in several cellular processes and implicated in human diseases. Autophagy is one of major cellular degradative pathways, which plays important roles in lipid metabolism. Recent studies have shown that SIRT1 deacetylates autophagy-related genes, and the expressions of autophagic genes are altered in MI patients. Accordingly, we hypothesized that SIRT1 may be linked to the MI pathogenesis. In this study, the SIRT1 gene promoter were genetically analyzed in large cohorts of MI patients ($n = 327$) and controls ($n = 358$). The results showed that six single-nucleotide polymorphisms and 14 sequence variants were identified. Among these, five novel heterozygous variants (g.69643743Ins, g.69643840Ins, g.69643903G > C, g.69644235G > C and g.69644353G > T) and one single-nucleotide polymorphism (rs35706870) were identified in MI patients, but in none of controls. Moreover, five novel heterozygous variants (g.69643672G > A, g.69644226C > T, g.69644278A > G, g.69644408G > A and g.69644408G > T) were only found in controls. The rest variants were found in MI patients and controls with similar frequencies. Taken together, the variants identified in MI patients may alter the transcriptional activities of SIRT1 gene promoter, which may change SIRT1 levels, contributing to the MI pathogenesis as a risk factor.

1. Introduction

Coronary artery disease is a common complex disease that is caused by interactions of environmental and genetic factors. Myocardial infarction (MI) is a restrictive phenotype of coronary artery disease. The established traditional risk factors include age, family history, hypercholesterolemia, hypertension, diabetes mellitus, smoking and obesity. To date, more than a dozen of genes and genetic loci related to MI have been identified with candidate gene, linkage analysis and genome-wide association studies [1–3]. However, the genetic causes and underlying molecular mechanisms for MI remain largely unknown.

Sirtuis are NAD-dependent class III deacetylases, which are highly conserved from yeast to human [4]. Surtuins have been shown to expand lifespan in yeast, worm and fly. In mammals, seven members of sirtuin family, SIRT1–SIRT7, have been identified, which have different cellular locations, enzyme activities, substrates and tissue-specific functions. SIRT1 is localized in the nucleus and the cytoplasm, and plays a critical role in epigenetic regulation by deacetylating histones. Moreover, SIRT1 interacts and deacetylates a broad set of transcription factors and regulators to control downstream gene expression. Many studies have demonstrated that SIRT1 is involved in cell survival and differentiation, genomic stability, transcription, metabolism, stress response and aging. Clinically, SIRT1 has been implicated in inflammation, obesity, type 2 diabetes, cardiovascular diseases, neurodegenerative disease and cancer [5–8].

In cultured cardiomyocytes and animal hearts, SIRT1 plays a protective role by acting against oxidative stress, inhibiting apoptosis, and inducing autophagy [9–11]. For example, SIRT1 activity

Abbreviations: ATG, autophagy-related gene; CREB, cAMP response element-binding protein; FOXO, forkhead box transcription factor; LC3, microtubule-associated protein 1 light chain 3 alpha; MI, myocardial infarction; SIRT1, Surtuin 1; SNP, single nucleotide polymorphism; TESS, transcription element search system.

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is necessary for protecting the heart from oxidative stress, myocardial ischemia and reperfusion [12,13]. In model animals and patients with dilated cardiomyopathy, activation of SIRT1 promotes cardiomyocytes survival [14]. In failing heart, SIRT1 gene overexpression inhibits apoptosis in cardiomyocytes [15,16]. SIRT1 has been shown to induce autophagy by deacetylating autophagy-related (ATG) proteins (ATG5 and ATG7) and forkhead box O transcription factors (FOXOs) [17,18]. In addition, SIRT1 also regulates endothelial angiogenesis and atherosclerosis [19,20].

Mice with SIRT1-null deletion die perinatally with severe heart defects [21,22]. In transgenic mice expressing SIRT1 gene in the heart, moderate elevation of SIRT1 protects cardiomyocytes, and high elevation of SIRT1 decreases cardiac function and causes cardiomyopathy [23]. Furthermore, constitutive overexpression of SIRT1 gene impairs cardiac function [24]. Collectively, SIRT1 functions in the heart in a dose-dependent manner. Furthermore, decreased autophagy activity has been observed in MI patients [25]. Therefore, we hypothesized that changed SIRT1 levels, rather than mutations in SIRT1 gene that change its amino acids, may contribute to the MI pathogenesis by interrupting autophagy. In this study, we genetically analyzed the SIRT1 gene promoter in large cohorts of MI patients and healthy controls.

2. Materials and methods

2.1. Study subjects

All MI patients (n = 327, mean age 60.70 years, male 229, female 98) were recruited from the Intensive Care Unit, Division of Cardiology, Jining Medical University Affiliated Hospital, Jining Medical University, Jining, Shandong, China. All MI patients were diagnosed with clinical symptoms, abnormal ECG findings and elevated levels of plasma cardiac necrosis markers. The ethic-matched healthy controls (n = 358, mean age 49.16 years, male 212, female 146) were recruited from Physical Examination Center in the same hospital. The controls with family histories of coronary artery disease were excluded. This study was approved by the Human Ethic Committee of Jining Medical University Affiliated Hospital and informed consents were obtained.

2.2. Genetic analysis

Genomic DNAs were extracted from peripheral leukocytes with DNeasy blood and tissue Kit (Qiagen, Valencia, CA, USA). The SIRT1 gene promoter, from −841 bp upstream to + 237 bp downstream to the transcription start site, was analyzed by direct sequencing. The genomic DNAs (100 ng) were used as PCR templates. Two overlapped DNA fragments covering the SIRT1 gene promoter, −841 bp to −321 bp (521 bp) and −355 bp to + 327 bp (592 bp), were generated by PCR. The primers were designed with the genomic sequence of human SIRT1 gene (Genebank access number, NC_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 sequencing was performed with 3730 DNA Analyzer (Applied Biosystems, Foster city, CA, USA). The DNA sequences were aligned and compared with wild type SIRT1 gene promoter. The distributions of sequence variants were compared between MI patients and controls using SPSS vs. 13.0. $P < 0.05$ was considered statistically significant.

3. Results

The distribution of the sequence variants within SIRT1 gene promoter were summarized in Table 1. Six single-nucleotide

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

Sequence variants	Genotypes	Location[1] (bp)	MI (n = 327)	Controls (n = 358)	P value
g.69643672G > A	GA	−855	0	1	–
g.69643707A > C(rs35706870)	AC	−820	3	0	–
g.69643743Ins	−/Ins	−684	1	0	–
g.69643840Ins	−/Ins	−588	1	0	–
g.69643903G > C	GC	−524	1	0	–
g.69643959A > G(rs3740051)	AA	−468	191	235	0.195
	AG		126	113	
	GG		10	10	
g.69644133C > G	CG	−334	2	2	0.928
g.69644213G > A	GA	−214	1	5	0.220
g.69644217A > C(rs932658)	AA	−210	220	230	0299
	AC		103	118	
	CC		4	10	
g.69644219G > A	GG	−208	323	347	0.181
	GA		4	10	
	AA		0	1	
g.69644226C > T	CT	−201	0	1	
g.69644235G > C	GC	−192	1	0	–
g.69644240G > T(rs35995735)	GG	−187	320	342	0.163
	GT		7	15	
	TT		0	1	
g.69644278A > G	AG	−149	0	1	–
g.69644335A > G(rs3740053)	AA	−92	186	221	0.385
	AG		129	123	
	GG		12	14	
g.69644341G > C(rs2394443)	GG	−86	218	230	0.387
	GC		104	119	
	CC		5	9	
g.69644351G > A	GA	−76	4	5	1.000
g.69644353G > T	GT	−74	1	0	–
g.69644408G > A	GA	−19	0	1	–
g.69644408G > T	GT	−19	0	1	–

[1] Locations of variants upstream (−) to the transcription start site of SIRT1 gene at 69644427 of NC_000010.

polymorphisms (SNPs) and 14 sequence variants were identified. Among them, five novel heterozygous variants (g.69643743Ins, g.69643840Ins, g.69643903G > C, g.69644235G > C and g.69644353G > T) were found in five MI patients, but in none of controls. Moreover, one SNP (g.69643707A > C, rs35706870) was found in three MI patients, but in none of controls. In contrast, five novel heterozygous variants (g.69643672G > A, g.69644226C > T, g.69644278A > G, g.69644408G > A and g.69644408G > T) were only identified in controls (Fig 1). In addition, the rest SNPs (rs3740051, rs932658, rs35995735, rs3740053 and rs2394443) and sequence variants (g.69644133C > G, g.69644213G > A, g.69644219G > A and g.69644351G > A) were found in MI patients and controls with similar frequencies (P > 0.05).

Analysis of SIRT1 gene promoter with transcription element search system (TESS, University of Pennsylvania) suggested that the variants identified in MI patients may change the putative

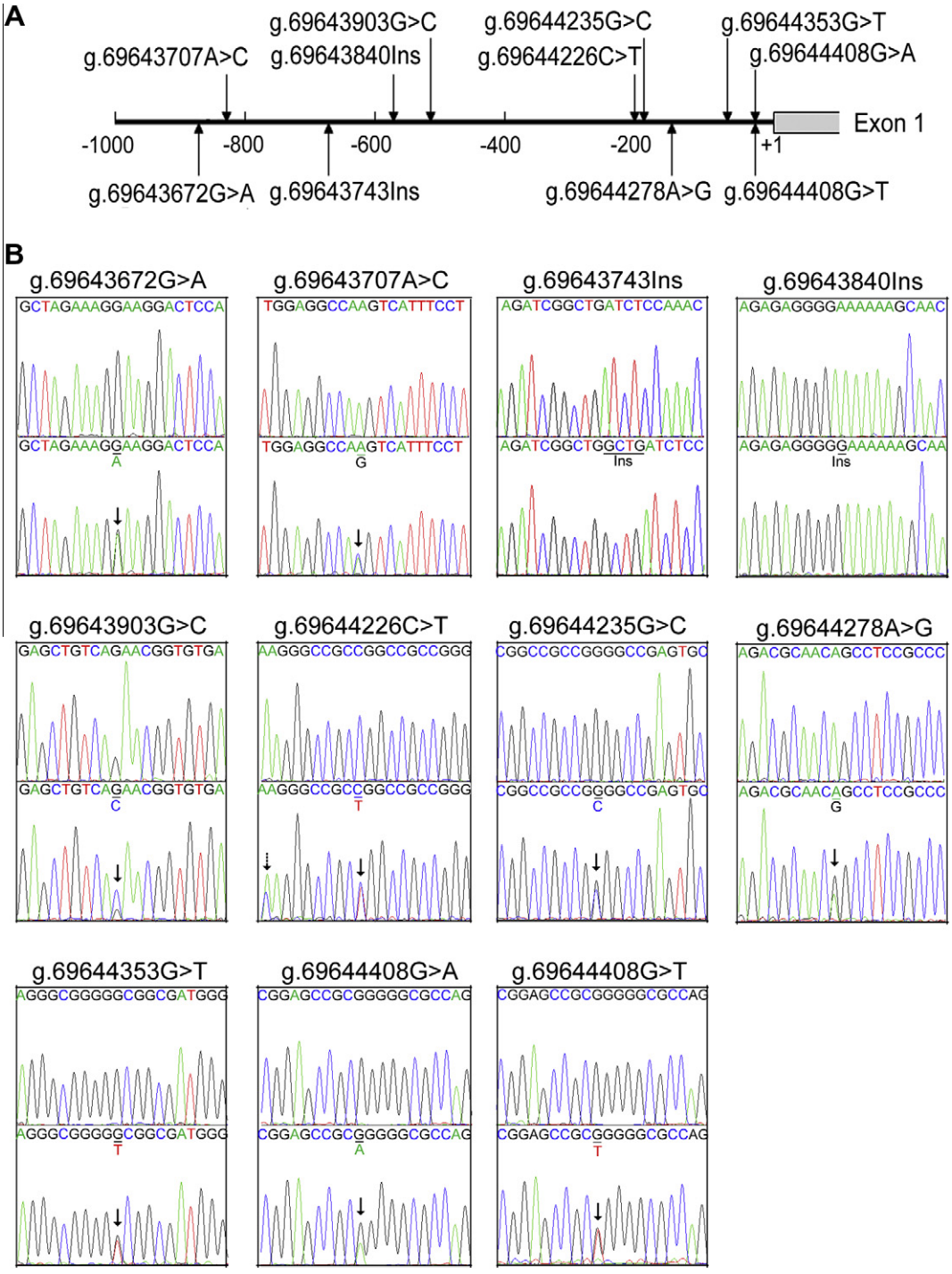

Fig. 1. The sequence variants identified within the SIRT1 gene promoter in MI patients and controls. (A) Schematic representation of the sequence variants within the SIRT1 gene promoter. The numbers represents the sequence of SIRT1 genomic sequences (Genebank accession number NC_000010). The sequence variants, only identified either in MI patients or controls, were depicted. The transcription starts at the position of 69644427 of the first exon. (B) Chromatograms of the sequence variants in forward orientations. The variants identified only in MI patients or controls were depicted. 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 g.69644226C > T, was indicated with a dashed arrow.

transcription factor binding sites, leading to altered transcriptional activity of the SIRT1 gene promoter.

4. Discussion

In this study, we genetically analyzed the SIRT1 gene promoter in large cohorts of MI patients and healthy controls. As expected, five novel heterozygous sequence variants and one SNP were found in MI patients, but in none of controls. Further TESS analyses suggested that the binding sites of transcription factors within the SIRT1 gene promoter may be changed by the variants, leading to changed SIRT1 level and contributing to the MI pathogenesis as a risk factor. Therefore, our data for the first time linked the sequence variants within SIRT1 gene promoter to MI patients.

Human SIRT1 gene is localized to the chromosome region 10q21.3 [26,27]. The SIRT1 gene is widely expressed in fetal and adult tissues, relatively high in the heart [28]. SIRT1 gene is regulated by a set of transcriptional factors and regulators, including CREB (cAMP response element-binding protein) and FOXOs [29,30]. Clinical studies suggest that the SNPs and variants in SIRT1 gene increase the risk of obesity and type 2 diabetes [31,32]. SIRT 1 polymorphisms have also been associated with abnormal cholesterol metabolism and coronary artery calcification [33]. In our previous studies with genetic analysis of the SIRT1 gene promoter, three heterozygous variants (g.69644133C > G, g.69644213G > A and g.69644351G > A) have been identified in sporadic Parkinson's disease, and four novel heterozygous variants (g.69643693A > G, g.69643963A > T, g.69643971G > A and g.69644366Ins) have been identified in patients with ventricular septal defects [34,35]. However, the above variants were not found or of no clinical significance in MI patients. Taken together, the different SNPs and variants were identified in diverse human diseases, indicating that the tissue-specific transcription factors that control SIRT1 gene expression are responsible for the disease pathogenesis.

Autophagy is a highly conserved cellular process, which delivers its components to lysosomes for degradation [36]. Autophagy is essential to many developmental and cellular processes and has been implicated in human diseases [37–39]. Macroautophagy (hereafter referred to as autophagy), the major subtype of autophagy, has been involved in lipid metabolism [40]. Microtubule-associated protein 1 light chain 3 (LC3), the autophagy marker gene, directly regulates the formation of lipid droplets in cells [41]. In mice, autophagy has been shown to protect cardiomyocytes from ischemic death during acute myocardial infarction [42]. Dysfunctional autophagy promotes atherosclerosis in part through induction of inflammation [43]. Several lines of evidence indicate that SIRT1 induces autophagy by deacetylating ATG proteins and FOXO factors [17,18,44]. Therefore, reduced SIRT1 may decrease autophagy activities, which interfere with lipid metabolism, contributing to the MI pathogenesis.

Recent studies have demonstrated that SIRT1 regulates adipogenesis and lipid metabolism by deacetylating transcription factors and regulators. In the fasting state, SIRT1 interacts with peroxisome proliferator-activated receptor γ coactivator 1α to promote fatty acid oxidation [45,46]. SIRT1 inhibits adipogenesis by repressing the transcriptional activity of peroxisome proliferator-activated γ receptor [47]. In liver, SIRT1 regulates lipid metabolism by activating liver X receptors and farnesoid X receptors [48–50]. In the heart, SIRT1 controls the cardiac hypertrophy, fatty acid metabolism, and inflammation processes by associating with peroxisome proliferator-activated α receptors [51]. Therefore, changed SIRT1 levels may be linked to the MI pathogenesis through lipid metabolism, inflammation and other pathways.

In conclusion, we genetically analyzed the SIRT1 gene promoter in MI patients. The novel sequence variants within the SIRT1 gene promoter identified in MI patients may contribute to the MI pathogenesis by changing SIRT1 levels. Since natural and pharmacological compounds have been identified for regulating SIRT1 activities [52,53], our findings may provide a genetic basis for potential personalized therapy for MI patients.

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References

[1] S. Kathiresan, D. Srivastava, Genetics of human cardiovascular disease, Cell 148 (2012) 1242–1257.
[2] K. Musunuru, S. Kathiresan, Genetics of coronary artery disease, Annu. Rev. Genomics Hum. Genet 11 (2010) 91–108.
[3] H. Schunkert, J. Erdmann, N.J. Samani, Genetics of myocardial infarction: a progress report, Eur. Heart J. 31 (2010) 918–925.
[4] 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.
[5] T. Finkel, C.X. Deng, R. Mostoslavsky, Recent progress in the biology and physiology of sirtuins, Nature 460 (2009) 587–591.
[6] M.C. Haigis, D.A. Sinclair, Mammalian sirtuins: biological insights and disease relevance, Annu. Rev. Pathol. 5 (2010) 253–295.
[7] 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.
[8] R.H. Houtkooper, E. Pirinen, J. Auwerx, Sirtuins as regulators of metabolism and healthspan, Nat. Rev. Mol. Cell Biol. 13 (2012) 225–238.
[9] N.R. Sundaresan, V.B. Pillai, M.P. Gupta, Emerging roles of SIRT1 deacetylase in regulating cardiomyocyte survival and hypertrophy, J. Mol. Cell. Cardiol. 51 (2011) 614–618.
[10] M. Tanno, A. Kuno, Y. Horio, T. Miura, Emerging beneficial roles of sirtuins in heart failure, Basic Res. Cardiol. 107 (2012) 273.
[11] T. Yamamoto, J. Sadoshima, Protection of the heart against ischemia/reperfusion by silent information regulator 1, Trends Cardiovasc. Med. 21 (2011) 27–32.
[12] C.P. Hsu, P. Zhai, T. Yamamoto, et al., Silent information regulator 1 protects the heart from ischemia/reperfusion, Circulation 122 (2010) 2170–2182.
[13] M. Vinciguerra, M.P. Santini, C. Martinez, et al., MIGF-1/JNK1/SirT1 signaling confers protection against oxidative stress in the heart, Aging Cell 11 (2012) 139–149.
[14] M. Tanno, A. Kuno, T. Yano, et al., Induction of manganese superoxide dismutase by nuclear translocation and activation of SIRT1 promotes cell survival in chronic heart failure, J. Biol. Chem. 285 (2010) 8375–8382.
[15] R.R. Alcendor, L.A. Kirshenbaum, S. Imai, S.F. Vatner, J. Sadoshima, Silent information regulator 2alpha, a longevity factor and class III histone deacetylase, is an essential endogenous apoptosis inhibitor in cardiac myocytes, Circ. Res. 95 (2004) 971–980.
[16] C.J. Chen, W. Yu, Y.C. Fu, X. Wang, J.L. Li, W. Wang, Resveratrol protects cardiomyocytes from hypoxia-induced apoptosis through the SIRT1-FoxO1 pathway, Biochem. Biophys. Res. Commun. 378 (2009) 389–393.
[17] N. Hariharan, Y. Maejima, J. Nakae, J. Paik, R.A. Depinho, J. Sadoshima, Deacetylation of FoxO by Sirt1 Plays an Essential Role in Mediating Starvation-Induced Autophagy in Cardiac Myocytes, Circ. Res. 107 (2010) 1470–1482.
[18] I.H. Lee, L. Cao, R. Mostoslavsky, et al., A role for the NAD-dependent deacetylase Sirt1 in the regulation of autophagy, Proc. Natl. Acad. Sci. USA 105 (2008) 3374–3379.
[19] M. Potente, L. Ghaeni, D. Baldessari, et al., SIRT1 controls endothelial angiogenic functions during vascular growth, Genes Dev. 21 (2007) 2644–2658.
[20] Q.J. Zhang, Z. Wang, H.Z. Chen, et al., Endothelium-specific overexpression of class III deacetylase SIRT1 decreases atherosclerosis in apolipoprotein E-deficient mice, Cardiovasc. Res. 80 (2008) 191–199.
[21] 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.
[22] 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.
[23] R.R. Alcendor, S. Gao, P. Zhai, et al., Sirt1 regulates aging and resistance to oxidative stress in the heart, Circ. Res. 100 (2007) 1512–1521.
[24] T. Kawashima, Y. Inuzuka, J. Okuda, et al., Constitutive SIRT1 overexpression impairs mitochondria and reduces cardiac function in mice, J. Mol. Cell. Cardiol. 51 (2011) 1026–1036.
[25] G. Wu, L. Liu, J. Huang, et al., Alterations of autophagic-lysosomal system in the peripheral leukocytes of patients with myocardial infarction, Clin. Chim. Acta 412 (2011) 1567–1571.
[26] 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.
[27] 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.
[28] G. Afshar, J.P. Murnane, Characterization of a human gene with sequence homology to *Saccharomyces cerevisiae* SIR2, Gene 234 (1999) 161–168.
[29] S. Nemoto, M.M. Fergusson, T. Finkel, Nutrient availability regulates SIRT1 through a forkhead-dependent pathway, Science 306 (2004) 2105–2108.
[30] 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.
[31] 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.
[32] 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.
[33] 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.
[34] 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.
[35] J. Shan, S. Pang, H. Wanyan, W. Xie, X. Qin, B. Yan, Genetic analysis of the SIRT gene promoter in ventricular septal defects, Biochem. Biophys. Res. Commun. (2012), in press.
[36] B. Ravikumar, S. Sarkar, J.E. Davies, et al., Regulation of mammalian autophagy in physiology and pathophysiology, Physiol. Rev. 90 (2010) 1383–1435.
[37] B. Levine, G. Kroemer, Autophagy in the pathogenesis of disease, Cell 132 (2008) 27–42.
[38] B. Levine, N. Mizushima, H.W. Virgin, Autophagy in immunity and inflammation, Nature 469 (2011) 323–335.
[39] N. Mizushima, M. Komatsu, Autophagy: renovation of cells and tissues, Cell 147 (2011) 728–741.
[40] R. Singh, S. Kaushik, Y. Wang, et al., Autophagy regulates lipid metabolism, Nature 458 (2009) 1131–1135.
[41] M. Shibata, K. Yoshimura, H. Tamura, et al., LC3, a microtubule-associated protein1A/B light chain3, is involved in cytoplasmic lipid droplet formation, Biochem. Biophys. Res. Commun. 393 (2010) 274–279.
[42] H. Kanamori, G. Takemura, K. Goto, et al., Autophagy limits acute myocardial infarction induced by permanent coronary artery occlusion, Am. J. Physiol. Heart Circ. Physiol. 300 (2011) H2261–2271.
[43] B. Razani, C. Feng, T. Coleman, et al., Autophagy links inflammasomes to atherosclerotic progression, Cell. Metab. 15 (2012) 534–544.
[44] A. Salminen, K. Kaarniranta, SIRT1: regulation of longevity via autophagy, Cell. Signal. 21 (2009) 1356–1360.
[45] Z. Gerhart-Hines, J.T. Rodgers, O. Bare, et al., Metabolic control of muscle mitochondrial function and fatty acid oxidation through SIRT1/PGC-1alpha, EMBO J. 26 (2007) 1913–1923.
[46] 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.
[47] F. Picard, M. Kurtev, N. Chung, et al., Sirt1 promotes fat mobilization in white adipocytes by repressing PPAR-gamma, Nature 429 (2004) 771–776.
[48] X. Hou, S. Xu, K.A. Maitland-Toolan, et al., SIRT1 regulates hepatocyte lipid metabolism through activating AMP-activated protein kinase, J. Biol. Chem. 283 (2008) 20015–20026.
[49] J.K. Kemper, Z. Xiao, B. Ponugoti, et al., FXR acetylation is normally dynamically regulated by p300 and SIRT1 but constitutively elevated in metabolic disease states, Cell. Metab. 10 (2009) 392–404.
[50] X. Li, S. Zhang, G. Blander, J.G. Tse, M. Krieger, L. Guarente, SIRT1 deacetylates and positively regulates the nuclear receptor LXR, Mol. Cell. 28 (2007) 91–106.
[51] A. Planavila, R. Iglesias, M. Giralt, F. Villarroya, Sirt1 acts in association with PPARα to protect the heart from hypertrophy, metabolic dysregulation, and inflammation, Cardiovasc. Res. 90 (2011) 276–284.
[52] A. Camins, F.X. Sureda, F. Junyent, et al., Sirtuin activators: designing molecules to extend life span, Biochim. Biophys. Acta 1799 (2010) 740–749.
[53] S. Lavu, O. Boss, P.J. Elliott, P.D. Lambert, Sirtuins–novel therapeutic targets to treat age-associated diseases, Nat. Rev. Drug Discov. 7 (2008) 841–853.