Abstract—Sirt7 is a member of the mammalian sirtuin family consisting of 7 genes, Sirt1 to Sirt7, which all share a homology to the founding family member, the yeast Sir2 gene. Most sirtuins are supposed to act as histone/protein deacetylases, which use oxidized NAD in a sirtuin-specific, 2-step deacetylation reaction. To begin to decipher the biological role of Sirt7, we inactivated the Sirt7 gene in mice. Sirt7-deficient animals undergo a reduction in mean and maximum lifespans and develop heart hypertrophy and inflammatory cardiomyopathy. Sirt7 mutant hearts are also characterized by an extensive fibrosis, which leads to a 3-fold increase in collagen III accumulation. We found that Sirt7 interacts with p53 and efficiently deacetylates p53 in vitro, which corresponds to hyperacetylation of p53 in vivo and an increased rate of apoptosis in the myocardium of mutant mice. Sirt7-deficient primary cardiomyocytes show a ≈200% increase in basal apoptosis and a significantly diminished resistance to oxidative and genotoxic stress suggesting a critical role of Sirt7 in the regulation of stress responses and cell death in the heart. We propose that enhanced activation of p53 by lack of Sirt7-mediated deacetylation contributes to the heart phenotype of Sirt7 mutant mice. (Circ Res. 2008;102:703-710.)

Key Words: sirtuin • aging • inflammation • stress resistance • hypertrophy

Sirtuins constitute a recently identified mammalian family of regulatory molecules (Sirt1 to Sirt7) that have been implicated in the control of critical cellular processes such as differentiation, proliferation, apoptosis, metabolism, and senescence. The best-characterized sirtuin, Sirt1, encodes for NAD-dependent deacetylase, which deacetylates histones and several regulatory proteins such as MyoD, p53, nuclear factor kB, and others. Inhibition of Sirt1 activity in cardiomyocytes leads to an increase in the basal rate of apoptosis and upregulation of hypertrophy-associated genes. The decrease of Sirt1 activity correlates with a higher acetylation of the cellular regulator p53, whereas dominant-negative p53 abolishes the effects caused by reduction of Sirt1 activity. In contrast, upregulation of Sirt1 seems to have a safeguarding effect, as indicated by the protection of cultured cardiac myocytes against isoproterenol-induced injury. Recently, transgenic mice have been established that overexpress Sirt1 in heart and skeletal muscles. Moderate overexpression of Sirt1 (2.5- to 7-fold increase above the endogenous Sirt1 expression level) protects against oxidative stress and age-dependent cardiac dysfunction. Interestingly, higher expression levels of Sirt1 (>9-fold) lead to apoptosis and hypertrophy and decreased cardiac function, suggesting a rather narrow window of optimal Sirt1 activity. The importance of a tightly controlled expression of Sirt1 for normal heart function and development is also demonstrated by the occurrence of heart abnormalities in Sirt1 mutant mice, whereas the relevance of Sirt1 for the function of adult hearts could not be approached to date because of the early postnatal lethality of Sirt1 mutants.

Very little is known about the role of other sirtuin family members in the heart. In this study, we have begun to unravel the biological function of Sirt7. Sirt7 is the only mammalian sirtuin, which is localized predominantly in the nucleoli; during mitosis, when the nucleoli disintegrate, Sirt7 associates with condensed chromosomes. Recent studies indicated that Sirt7 binds to RNA polymerase I and activates ribosomal (r)RNA-encoding DNA (rDNA) transcription. This unexpected finding is in sharp contrast to the silencing function of the family founder, the yeast Sir2, on rDNA chromatin. Whether Sirt7 activates rDNA transcription in vivo awaits further evaluation, because this function was only demonstrated in cultured cell lines by overexpressing or knocking down Sirt7. Interestingly, an elevated Sirt7 expression has been detected in several human cancers. The molecular targets and potential enzymatic activity of Sirt7 have not been identified yet.

Using targeted mutagenesis in mice, we show here that Sirt7 plays an important protective role in the adult myocardium.
Sirt7-deficient mice develop progressive heart hypertrophy, accompanied by inflammation and decreased stress resistance. At least a part of this phenotype may be explained by our finding that Sirt7 deacetylates p53, leading to hyperacetylation of p53 in vivo along with various other changes in the signaling network of cardiomyocytes.

**Materials and Methods**

**Mice**

Generation of the Sirt7-targeting construct, homologous recombination in embryonic stem cells, and generation of Sirt7 knockout mice followed established procedures as described previously. Knockout animals were backcrossed to a C57Bl/6 genetic background. No phenotypic differences were detected in the first generation animals on mixed C57Bl/6 and 129Sv background, which were used for some initial analyses. For all studies, male littermates, which were kept under the same conditions, were used. All procedures were performed in accordance with the guidelines for animal experimentation of the local authorities.

**Fluorescence-Activated Cell-Sorting Analysis**

Blood cells were characterized by standard flow cytometry as described using PE-conjugated antibodies against CD3, CD4, CD8, CD19. Data collected from >10,000 cells were expressed as the percentage of positive cells per total gated cells. Raw data were analyzed using the CellQuest pro software (BD Inc.).

**Cell Culture**

Primary cardiomyocytes were cultured under standard conditions as described; primary hepatocytes were isolated from perfused livers according to published protocols.

**Deacetylation Assay**

Deacetylation activity of recombinant mouse Sirt1 and Sirt7 protein was estimated using acetylated p53 peptides (p53–382/diAc) and a Sirt1 Fluorometric Drug Discovery kit (AK-555) according to the protocol of the manufacturers (BIOMOL).

**Apoptosis**

Apoptotic cardiomyocytes on heart tissue sections and in culture were visualized using TUNEL staining and analyzed by confocal laser scanning microscopy as described previously.

**Western Blotting**

Protein lysates (10 μg) were separated on 4% to 12% SDS-PAGE gradient gels and transferred onto nitrocellulose membranes (Invitrogen Life Technologies). Immunoreactive proteins were visualized with corresponding horseradish peroxidase–conjugated secondary antibodies on Hyperfilm (GE Healthcare) using the SuperSignal West Pico or West Femto detection solutions (Perbio Science). Antibodies directed against p-PTEN, total PTEN, p-Akt, total Akt, Ras, pan-actin, β-tubulin, and Fas/CD95 were from NEB (Cell Signaling) and c-Raf was from Becton Dickinson. Anti-actin and anti-tubulin antibodies served as loading controls.

**Immunohistochemistry**

Tissues for immunohistochemistry were fixed and either embedded in paraffin or shock-frozen for cryosectioning and processed as described previously. Monoclonal antibodies against smooth muscle α-actin and skeletal α-actin were purchased from Sigma, those against CD68 were from Santa Cruz Biotechnology, and polyclonal antibodies against collagen III and VI were from Rockland.

**Transmission Electron Microscopy**

Tissues were fixed with 4% glutaraldehyde (Merck), followed by 4% OsO4. After dehydration in alcohol, they were embedded in Epon according to routine procedures. Semithin sections (1-μm) sections were stained with toluidine blue and viewed in a Leica DM microscope. Ultrathin sections were stained with uranyl acetate and lead citrate and viewed and photographically recorded under a Philips CM 10 electron microscope.

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**Figure 1.** Generation of Sirt7-deficient mice.

a. Expression of Sirt7 and the cardiomyocytes-specific troponin T in heart tissues at different stages of adult life (n=3) as determined by real-time quantitative RT-PCR (*P<0.05). b. Representation of genomic Sirt7 regions used for construction of the targeting vector for homologous recombination in embryonic stem cells. c. Southern blot analysis of wild-type, Sirt7 heterozygous, and Sirt7-deficient animals; the 11.5-kb EcoRV band represents the wild-type allele, which is converted to 6.5-kb fragment after homologous recombination. d. Kaplan–Meier survival curve showing a reduced lifespan of Sirt7 knockout mice. Note that both the mean and the maximal lifespan are decreased; n=98 (wt) and n=32 (KO).
Quantitative Real-Time PCR
Tissue RNA was isolated using the TRIzol method, and quantitative RT-PCR was performed as described. Sequences for primer sets and further details are available from the authors on request.

Statistics
Statistical analyses were performed using the Student’s *t* test.

Results

Generation of Sirt7-Deficient Mice
In a search for genes that may be involved in functional deterioration of the heart during aging, we performed extensive comparative gene expression profiling of aging hearts of different rodent species using Affymetrix GeneChip DNA microarrays (detailed results of the chip expression analysis will be presented elsewhere). We found that the group of genes, which displayed a robust reduction of expression during aging, contained Sirt7, a member of the sirtuin family of genes implicated in the regulation of aging processes.

To verify age-dependent changes of Sirt7 expression, we determined Sirt7 mRNA levels in heart tissues from animals of different ages using quantitative RT-PCR analysis. During the first year of life, Sirt7 expression was kept at a relatively constant level. Old mice, at 23 months of age, showed a rather different picture, which was characterized by a 40% decrease of the Sirt7 expression (Figure 1a). The same tissue samples revealed no age-dependent changes of the troponin T mRNA, in agreement with previously published data (Figure 1a).

The decreased level of Sirt7 expression in aging heart tissue suggested that Sirt7 may be important to contribute to cellular signaling processes required for the maintenance of normal heart functions. To analyze the Sirt7 function in the heart in vivo, we generated Sirt7-deficient mice. The strategy for inactivation of the Sirt7 gene is outlined in Figure 1b. Homologous recombination resulted in deletion of the putative deacetylase domain encoded by exons 4 to 9, as monitored by Southern blot analysis (Figure 1b and 1c). We also confirmed the lack of Sirt7 mRNA in homozygous mutant hearts by quantitative RT-PCR and Northern blot analysis (data not shown). No obvious phenotype was observed in heterozygous mutant Sirt7 animals, whereas homozygous mutants showed various signs of aging-related changes and died prematurely. The mean and maximum lifespan of Sirt7-deficient mutants was reduced by 59% and 55%, respectively (Figure 1d). Mutant mice developed kyphosis and lost subcutaneous fat early in life; they also showed a general decrease in stress-resistance mechanisms (Olesya Vakhrusheva, Christian Smolka, Thomas Braun, and Eva Bober, manuscript in preparation).

Sirt7 Knockout Mice Suffer From Degenerative Heart Hypertrophy
Analysis of heart weight to body weight (HW/BW) ratio in knockout (n=6) and wild-type animals (n=7) revealed no changes in newborn Sirt7-deficient animals (Figure 2a). In young animals (2.5 to 3 months of age), a slight increase in HW/BW ratio was detected in knockout (n=8) as compared to wild-type controls (n=6), although this change was not statistically significant (Figure 2a). At the age of 7 to 11 months (n=7 for the wild-type and n=8 for the knockout mice), the hypertrophy became more pronounced, as indicated by a statistically significant increase of the HW/BW ratio (*P*<0.005; Figure 2a). Hypertrophic changes in Sirt7 mutant hearts were further confirmed on histological sections from knockout and wild-type hearts. Staining with γ-sarcoglycan indicated an enlargement of the majority of cardiomyocytes, with strong caliber variations reflecting ongoing cardiac remodeling (Figure 2b and 2c). A quantitative assessment of the cross-sectional areas of cardiomyocytes on γ-sarcoglycan–stained sections (Figure 2b and 2c) revealed that all wild-type cardiomyocytes possessed a mean diameter of 17±4 μm, whereas the diameter of Sirt7 mutant cardiomyocytes showed a bimodal distribution: the majority of mutant cardiomyocytes (68±2%) were characterized by a mean diameter of 32±3 μm, whereas a smaller group (32±3%) displayed a strong reduction (mean diameter of 6±2 μm). Degenerative changes in Sirt7 mutant hearts were also reflected by a strong increase of fibrosis, as indicated by

![Figure 2. Degenerative heart hypertrophy in Sirt7-deficient mice.](image-url)
collagen VI accumulation (Figure 2d and 2e) and the repression of smooth muscle α-actin in cardiomyocytes (Figure 2f and 2g). To evaluate the fibrotic changes accompanying the heart hypertrophy in Sirt7−/− mice more precisely, a detailed analysis of the fibrillar collagen III was performed on 6-month-old (n=2) and 9-month-old (n=2) knockout hearts and compared with age-matched wild-type controls. Figure 2h through 2m illustrates the massive fibrosis present in a 9-month-old knockout specimen in comparison with the wild-type control. A quantitative analysis revealed that areas with collagen III deposition reached 18% of knockout myocardial tissue, whereas collagen III in wild-type controls covered an area <8% (Figure 2n).

Further morphological analysis of Sirt7-deficient myocardium by electron microscopy revealed enhanced accumulation of lipofuscin and an increased number of apoptotic cells (Figure 3). Lipofuscin inclusions, which are intralysosomal, polymeric, undegradable deposits that aggregate in aged tissues,21 were present in Sirt7-deficient cardiomyocytes but not in wild-type cardiomyocytes (Figure 3a and 3b). The rate of apoptosis was further analyzed in Sirt7 mutant hearts using TUNEL staining. We found an ≈200% increase of the number of cardiomyocytes undergoing apoptosis, as indicated by triple labeling for F-actin, 4′,6-diamidino-2-phenylindole (DAPI), and TUNEL staining (Figure 3g and 3h).

**Sirt7 Deacetylates p53 and Increases Resistance to Cytotoxic and Oxidative Stress in Neonatal Primary Cardiomyocytes**

The increase of apoptosis in hearts of Sirt7 mutants prompted us to investigate the activity of p53. p53 is regulated at the transcription level, by protein stability and by posttranslational modifications including protein acetylation, which leads to enhanced activity of the protein.22 We reasoned that Sirt7 may decrease p53 activity by deacetylation, leading to a protection of cardiomyocytes against apoptosis. To test this hypothesis, we first investigated whether Sirt7 deacetylates p53 in vitro. Indeed, p53 peptides were deacetylated by Sirt7 in vitro to an extent similar to Sirt1, which is a known deacetylase of p53 (Figure 4a). Addition of resveratrol, a polyphenolic compound, strongly increased both Sirt7- and Sirt1-dependent p53 deacetylation, whereas the sirtuin inhibitor suramin inhibited p53 deacetylation by Sirt1 and Sirt7 (Figure 4a). To demonstrate that deacetylation of p53 depended on the enzymatic activity of Sirt7, we introduced 2 point mutations into the catalytic domain of Sirt7, which nearly completely abolished deacetylation of p53 (Figure 4a).

To prove whether the increase of apoptosis in the myocardium was primarily caused by cell autonomous events in cardiomyocytes and not by infiltration of inflammatory cells (see below), we analyzed the degree of apoptosis in primary cardiomyocytes isolated from Sirt7 mutant mice. We found an ≈2-fold increase of the number of TUNEL-positive cardiomyocytes in culture; the cells were also stained for the cardiomyocyte marker α-actinin to confirm their identity (Figure 4c and 4d). These findings corresponded nicely with the increase in apoptosis that we observed in the myocardium.
of Sirt7−/− mice in vivo (Figure 3g and 3h). We next investigated whether cardiomyocytes derived from Sirt7 mutant mice were more susceptible to genotoxic or oxidative stress. Treatment of primary cardiomyocytes from Sirt7 mutant mice with either doxorubicin or hydrogen peroxide increased the number of apoptotic cells significantly, whereas apoptosis in wild-type cultures occurred only sporadically under these conditions (Figure 4c and 4d). It seems likely that cardiomyocytes of Sirt7 mutant mice are more susceptible to apoptosis because of a hyperactive p53 (see below).

Increased Inflammation and Inflammatory Cardiomyopathy in Sirt7-Deficient Heart
Because Sirt7 is broadly expressed, the question arose regarding extent to which the observed cardiac phenotype of Sirt7 mutants may be solely caused by depletion of Sirt7 in cardiomyocytes or whether additional mechanisms may contribute. It seemed possible that signals from Sirt7-deficient lymphocytes and macrophages do participate in the pathogenetic process, leading to the cardiac phenotype of Sirt7 mutant mice because susceptibility to inflammation rises progressively with age. This assumption was also supported by the relatively high expression level of Sirt7 in blood and in the lymphocytes. We therefore searched for signs of inflammation in Sirt7-deficient mice. Fluorescence-activated cell-sorting (FACS) analysis revealed increased numbers of granulocytes and T lymphocytes in the blood of Sirt7 mutant mice, although the increase in T lymphocytes did not reach statistical significance (Figure 5a). In particular, the number of granulocytes was increased by more than 3-fold, indicating ongoing inflammatory processes in mutant mice. Moreover, a histological analysis revealed inflammatory infiltrations in the myocardium of Sirt7−/− mice (Figure 5b and 5c). Immunostaining with a CD68 antibody, which specifically detects inflammatory macrophages, revealed that such cells were present at interstitial and perivascular locations (Figure 5d and 5e). We also detected an augmented cytokine levels in hearts of 2-month-old Sirt7-deficient animals (Figure 5f). The difference between cytokine levels in Sirt7 mutant and control hearts increased with age, as illustrated for 12-month-old animals in Figure 5g. The strongest changes were detected for the production of interleukin-12 and -13, which were increased by 200% and 300% when compared with wild-type controls (Figure 5f and 5g). Taken together, it seems likely that general inflammatory processes contribute to the heart phenotype of Sirt7 knockout mice, although we do not know at present whether the infiltration is among the primary causes of the phenotype or a consequence of degenerative changes in the myocardium.

Increased Hypertrophic and Apoptotic Signaling Pathways in Sirt7-Deficient Myocardium and in Primary Sirt7-Deficient Cardiomyocytes
It seemed likely that malfunctions in numerous signaling pathways contributed to the development of hypertrophy and inflammatory cardiomyopathy in hearts of Sirt7 mutant mice. We therefore investigated the activity of several different signaling pathways, which are known to play a role in the development of cardiac hypertrophy. One of the main regulators of physiological heart growth is AKT/PKB, which is also required for functional compensation during pressure overload. In addition, it has been demonstrated that AKT/PKB signaling is beneficial to the heart when it is acutely activated under physiological conditions but leads to hypertrophy and heart failure when chronically activated. Sirt7 mutant hearts showed only slightly increased levels of total Akt protein but a strong increase in activated (phosphorylated) Akt (Figure 6a). The Akt inhibitor and tumor suppressor molecule PTEN was found to be massively reduced in mutant hearts, as indicated by a strong reduction of the PTEN protein and an increase in inactivated (phosphorylated) PTEN. Interestingly, we also observed increased expression of 2 members of the Ras-Raf-MEK-ERK pathway, Ras and c-Raf (Raf1) (Figure 6a), which are well-known components of signal-transduction pathways that coordinate the cardiac hypertrophic responses. We also detected increased amounts of Fas/CD95 protein, suggesting that the external apoptosis pathway did contribute to the increased rate of apoptosis found in Sirt7 mutant hearts (Figure 6a), probably together with enhanced activity of hyperacetylated p53.
cardiomyocytes and to avoid contaminations that may result from activation of signaling pathways in infiltrating cells, we again used isolated cardiomyocytes. We found increased Akt phosphorylation and a slight increase of c-Raf protein level in isolated cardiomyocytes, which corresponds to the changes observed in whole organ extracts (Figure 6b). However, no increase in the death receptor Fas/CD95 was detected in the cardiomyocytes, which is in contrast to what was observed in the whole heart tissue, although cleavage of poly(ADP-ribose) polymerase, a downstream target of activated caspases, was strongly increased in Sirt7−/− cardiomyocytes (Figure 6b). Most interestingly, the level of acetylated p53 protein was significantly increased, as demonstrated by quantitative Western blot analysis (Figure 6b and 6c), further supporting our hypothesis that an increase in p53 activity mediated by Sirt7 may be the primary cause of increased apoptosis in Sirt7-deficient cardiomyocytes. The presence of other cell types in the heart probably did obscure detection in whole heart extracts.

**Discussion**

Mammalian sirtuins constitute a family of cellular regulators that are involved in preservation of organ functions during stress response and aging. Although the heart is among the primary target tissues that is affected by the continuous decline of the ability to respond to adverse conditions during aging, little is known about the role of sirtuins in this process.
and only Sirt7 has been investigated in this respect to date. In this study, we have demonstrated that Sirt7 plays an important role to prevent progressive functional deterioration of the heart. Sirt7 deletion led to various pathological changes in young adult hearts, which further aggravated with age. Changes included heart hypertrophy, fibrosis, lipofuscin accumulation, increased apoptosis under basal conditions and in response to oxidative, and genotoxic stress. It is interesting to note that Sirt1 may play a similar role as Sirt7 to protect heart from exaggerated stress responses that cause multiple types of damage, although its role in cardiac physiology could not be studied in vivo because of the early lethality of Sirt1-deficient mice. However, moderate overexpression of Sirt1 in transgenic animals decreases the baseline level of apoptosis, retards age-dependent malfunctions, and protects cardiomyocytes from oxidative stress–induced apoptosis, supporting the view that Sirt1 has a protective function for heart tissue maintenance and cardiac physiology.

It remains to be resolved whether Sirt1 and Sirt7 act synergistically or in parallel pathways. Our finding that both Sirt1 and Sirt7 deacetylate p53 argues for overlapping, possibly synergistic actions, at least with respect to the regulation of p53. Sirt1 was also postulated to protect cardiomyocytes from apoptosis through inactivation of p53 by deacetylation. Additional evidence that Sirt1 and Sirt7 may act together comes from studies on the expression of Sirt1 in failing hearts of human patients and from overexpression studies of Sirt1 in the mouse. Pillai et al detected reduced Sirt1 activity and higher levels of active, acetylated p53 in failing hearts of patients experiencing dilated ischemic cardiomyopathy. Intriguingly, massive overexpression of Sirt1 did not prevent, but rather stimulated, the appearance of degenerative changes in the heart. It is tempting to speculate that it is pivotal to maintain a specific ratio between Sirt1 and Sirt7 to ensure optimal target deacetylation and adequate biochemical signaling. An imbalance between Sirt1 and Sirt7 may result in exaggerated stress responses that cause multiple types of damage and prevents maintenance of a “youthful” homeostasis in the aging heart.

A decline of the expression of 3 sirtuins, Sirt3, Sirt7, and Sirt2, was discovered recently in aging hematopoietic stem cells (HSCs) and was linked to epigenetic regulation phenomena in such cells. The authors did also describe multiple similarities in age-dependent gene expression pattern between HSCs and postmitotic tissues, such as heart and skeletal muscle. Our finding that the expression of Sirt7 declines in aging hearts and that the absence of Sirt7 in mutant animals promotes a phenotype, which is reminiscent of several changes observed in aging hearts, is in line with these results and asks for similar mechanisms that contribute to aging of HSC and the heart. It will be interesting to investigate the role of Sirt7 for regeneration in different stem cell populations including the hematopoietic system and the heart.

So far, very little is known about Sirt7 targets and the molecular details of its action. In a recent study, Ford et al claimed that Sirt7 is an activator of RNA–polymerase I transcription based on the association of Sirt7 with rDNA and RNA–polymerase I and the activation of rDNA transcription in cells overexpressing Sirt7. Unlike our study, which clearly defines p53 as a direct target of Sirt7, no enzymatic activity was reported that may account for this function, although point mutations of conserved residues within the deacetylase domain abolished activation of RNA–polymerase I transcription. The authors also described induction of cell proliferation, along with the stimulation of RNA–polymerase I transcription and increased rRNA biosynthesis. The phenotype of Sirt7 mutant mice described here is clearly not compatible with these results. We found that Sirt7 prevents Ras and Akt activation in vivo (Figure 6d), although both pathways lead to increased rRNA biosynthesis for example via activation of the mTOR signaling. Furthermore, we did not find a hint for decreased rRNA biosynthesis or reduced cell proliferation in various different tissues (data not shown). These conflicting results may be explained by the different cellular and experimental settings in which the effects of Sirt7 were monitored. In their study, Ford et al used the highly proliferative cell lines HEK293T and NIH3T3 and massive overexpression of Sirt7, whereas we have obtained most of our results in a primarily postmitotic tissue such as the heart. It is clearly necessary to obtain a refined view of the role of Sirt7 and other sirtuins in the regulation of proliferation.
because also the function of Sirt1 in the control of proliferation is controversial.  

In summary, we have established that Sirt7 is an essential regulator of tissue homeostasis in the heart. We postulate that this function becomes increasingly important during aging, when general maintenance mechanisms gradually fail and regulatory networks deteriorate. We reason that optimization and stabilization of the interplay between regulators of tissue homeostasis and stress responses may offer a therapeutic approach to ease and/or delay consequences of functional deterioration of the heart.

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Disclosures

None.

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