Mice Deficient in Telomerase Activity Develop Hypertension Because of an Excess of Endothelin Production

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Background—Telomere shortening has been related to vascular dysfunction and hypertension. In the present study, we analyzed the influence of telomerase deficiency and telomere shortening on arterial pressure (AP).

Methods and Results—AP was evaluated in 6-month-old mice lacking the RNA component of the telomerase (terc\(^{-/-}\)) at the first generation and third generation (G3). First generation and G3 mice showed higher AP than wild-type (WT) mice. To analyze the mechanisms involved, mean AP and vascular resistance in response to vasoactive substances were measured in G3 and WT mice. These mice showed similar responses to acetylcholine, N\(^\circ\)-nitro-L-arginine methyl ester, angiotensin II, and losartan administration. Mean AP did not increase after endothelin-1 (ET-1) administration in G3 mice, but it did in WT animals. Bosentan treatment decreased mean AP only in G3 mice. Serum and urine concentrations of ET-1 were higher in terc\(^{-/-}\) than in WT mice. Endothelin-converting enzyme (ECE-1) mRNA expression was higher in terc\(^{-/-}\) animals than in the WT group. FR901533, an ECE antagonist, decreased blood pressure in conscious G3 mice. Studies in mouse embryonic fibroblasts from G3 mice suggest that ECE-1 overexpression could be mediated by reactive oxygen species in an AP-1–dependent mechanism, in which some kinases such as PI3-kinase, Akt, erk1/2, and Jun Kinase could be involved. An increased activity of nicotinamide adenine dinucleotide phosphate oxidase seems to be the main source of reactive oxygen species.

Conclusions—Mice lacking telomerase activity show hypertension as a result of an increase in plasma ET-1 levels, which is a consequence of ECE-1 overexpression. A direct link between telomerase activity and hypertension is reported.

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Key Words: aging ■ telomerase ■ hypertension ■ endothelin ■ endothelin-converting enzyme

Hypertension

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Hypertension is the most prevalent disorder in the elderly population. In fact, its prevalence is \(\approx 20\%\) to \(30\%\) in individuals between 30 and 50 years of age and increases to \(50\%\) in the eighth decade of life.1 Different mechanisms have been proposed to explain its genesis. First, morphological changes that take place at the vascular walls, promoted by the progressive stiffness, atherosclerotic process, and inflammatory response, could contribute to the development of increased vascular resistance.2 Moreover, aging leads to an impaired synthesis of endothelial bioactive factors, with subsequent endothelial dysfunction and relative vasoconstriction.3,4 Finally, the decreased glomerular filtration rate and renal plasma flow of elderly individuals,5 by interfering with sodium renal excretion, also could be involved in the onset of hypertension.

It has been proposed that cell senescence at vascular walls also could contribute to the development of vascular disor-
zyme composed of multiple subunits, among others an RNA molecule called TERC\textsuperscript{17} and a catalytic protein subunit called TERT.\textsuperscript{18} Telomerase, acting as a reverse transcriptase, produces telomeric repeats using a template provided by TERC.\textsuperscript{19}

Mice lacking telomerase activity (\textit{terc}\textsuperscript{−/−} or \textit{tert}\textsuperscript{−/−}) have been developed to study the role of this holoenzyme in aging and cancer.\textsuperscript{20,21} Knockout mice for the telomerase RNA component (\textit{terc}\textsuperscript{−/−}) show progressive telomere shortening in successive generations, with signs of premature aging between the third and sixth generations, depending on the genetic background.\textsuperscript{22} Infertility, abnormal hematologic profile with attenuated bone marrow stem cell proliferation, atrophy of small intestine and spleen, and decreased lifespan are phenotypic changes found in the fifth generation of the original mixed background.\textsuperscript{23,24} \textit{Terc}\textsuperscript{−/−} mice also show reduced angiogenic responses,\textsuperscript{25} attenuation of cardiac myocyte proliferation, increased apoptosis, and cardiac myocyte hypertrophy.\textsuperscript{26} However, mice from the first generation, without telomerase activity but with long telomeres, have normal phenotypes.\textsuperscript{21}

The main aim of the present study was to analyze the role of cell senescence in the regulation of blood pressure. Particularly, the influence of telomerase activity and telomere shortening was assessed. Moreover, the possible mechanisms involved were evaluated.

### Methods

#### Animals

Mice C57BL/6 lacking the gene encoding the telomerase RNA component (\textit{terc}\textsuperscript{−/−}) were generated as previously described.\textsuperscript{20} \textit{Terc}\textsuperscript{−/−} mice show progressive telomere shortening with increasing mouse generation, appearing as age-related pathologies from the third generation in the pure background.\textsuperscript{24} Animals with the same genetic background were used as controls. All the animals were housed in a pathogen-free and temperature-controlled room (22±2°C) under the standard conditions proposed by the European Union. Food and water were available ad libitum.

All the procedures were performed in 6-month-old mice. Three experimental groups were used: wild-type (WT) mice (body weight, 24.3±0.7 g), \textit{terc}\textsuperscript{−/−} first-generation (G1) mice lacking telomerase activity and with no significant telomere shortening (body weight, 19.9±1.0 g), and \textit{terc}\textsuperscript{−/−} third-generation (G3) mice lacking telomerase activity and with significant telomere shortening (body weight, 15.5±1.2 g).\textsuperscript{22} Each group had the same number of males and females. Mice were provided by María A. Blasco from Centro Nacional de Investigaciones Oncológicas (Madrid, Spain).

#### Studies in Conscious Animals and Sample Collection

Arterial pressure (AP) was measured in conscious animals by means of a tail-cuff sphygmomanometer (LE 5001 Pressure Meter, Letica Scientific Instruments, Hospitalet, Spain). Animals were trained for 3 days before starting the measurement to prevent stress and were prewarmed at 30°C with a heater (LE5660/6, Letica Scientific Instruments). One week later, mice were placed in metabolic cages for urine collection. Then, under halothane anesthesia, blood samples were obtained from the heart, centrifuged, and stored at −80°C. Immunoreactive endothelin-1 (ET-1) and endothelin-converting enzyme (ECE) were measured in these tissues by semiquantitative and real-time reverse-transcriptase (RT) polymerase chain reaction (PCR)\textsuperscript{27} (see the online Data Supplement). A subgroup of WT and G3 animals was treated with the ECE inhibitor FR901533 (C\textsubscript{27}H\textsubscript{21}NaO\textsubscript{10} [see the Data Supplement for the complete structure]; Fujisawa Pharmaceutical Co, Osaka, Japan) 1 mg/kg body weight IP, and AP was measured at various points during 90 minutes.

#### Studies in Anesthetized Animals

Changes in mean AP (MAP) and vascular resistances\textsuperscript{28} of WT and G3 mice were evaluated in response to acetycholine (Ach) iodine (0.4, 0.6, and 0.8 \(\mu\)g/kg body weight, Sigma Chemical, St Louis, Mo), N\textsuperscript{ω}-l-arginine methyl ester (L-NAME; 50 mg/kg, Sigma), angiotensin II (Ang II; 0.15 and 0.3 mg/kg body weight, Sigma), and losartan (10 mg/kg, Merck, Darmstadt, Germany). The effects of ET-1 (1 nmol/kg, Sigma) and bosentan (10 mg/kg body weight; a gift of Dr Martine Clozel, Actelion Ltd, Allschwil, Switzerland) were tested in WT, G1, and G3 mice. A detailed description of these methods is given in the online Data Supplement.

#### Studies in Mouse Embryonic Fibroblasts

Mouse embryonic fibroblasts (MEFs) were prepared from embryos of WT and G3 mice as previously described.\textsuperscript{16} ECE-1 protein...
expression was measured by Western blot in MEFs with a monoclonal anti–ECE-1 antibody (Sankyo Co, Tokyo, Japan). Thereafter, MEFs were transfected with a plasmid containing the promoter of human ECE-1 or with its consecutive deletion mutants linked to a luciferase reporter (see Data Supplement for details). Transfected MEFs were treated with 80 U/mL catalase (Sigma), 10 mmol/L N-acetyl cysteine (NAC; Sigma), 10 μmol/L diphenyleneiodonium chloride (DPI; nicotinamide adenine dinucleotide phosphate [NADPH] oxidase inhibitor; Sigma), 50 μmol/L PD98059 (erk1/2 inhibitor; Stressgen, Victoria, BC, Canada), 50 μmol/L specific Akt inhibitor (Calbiochem), 50 μmol/L wortmannin (PI3-kinase inhibitor; Sigma), 10 μmol/L SP 600125 (Jun Kinase [JNK] inhibitor; Stressgen), or 100 μmol/L hydrogen peroxide (H₂O₂, Sigma), and the promoter activity was assayed. Finally, reactive oxygen species (ROS) production was determined in MEFs by flow cytometry (see Data Supplement). Some experiments were performed in the presence of either DPI or the kinase inhibitors.

Statistical Analysis
Data are presented as mean±SEM of a variable number of experiments (see figure legends). For the analysis of repeated measures in the same animals, 2-way repeated-measures ANOVA (RMANOVA) was used. When the results showed no evidence of statistical interaction, the main effects for time and mouse genotype were reported. If a significant interaction was present, multiple post hoc pairwise comparisons between mouse genotypes at the same time point were performed. Bonferroni’s correction was used to adjust for multiple comparisons between mice groups (details of when this correction was applied are given in the figure legends). Two-way ANOVA and Mann-Whitney and Kruskal-Wallis tests were used to compare unpaired data. Again, a conservative Bonferroni approach was used to deal with multiple comparisons. All tests were 2 tailed, and a value of P<0.05 was regarded as statistically significant.

The authors had full access to the data and take full responsibility for their integrity. All authors have read and agree to the manuscript as written.

Results
AP values in conscious animals are shown in Figure 1A. G1 mice showed increased systolic AP (SAP) values compared with WT animals. Both SAP and diastolic AP (DAP) increased in G3 mice with respect to WT and G1 mice. The role of endothelial vasoactive factors and Ang II in the genesis of this hypertension was analyzed by hemodynamic studies in WT and G3 anesthetized animals. In basal conditions, the mice lacking telomerase activity showed higher systolic and diastolic blood pressure values than WT mice (Figure 1B). A good correlation was observed between the values of AP in anesthetized mice and those obtained by the tail-cuff method (r=0.86, P<0.01).

The role of nitric oxide (NO) in the development of hypertension was tested by modulating the NO endothelial synthesis with Ach and L-NAME. WT animals treated with increasing Ach concentrations showed a typical dose-response decrease in MAP (Figure 2A) and hindlimb vascular resistance (HVR; Figure 2B). Inhibition of NO with L-NAME induced a significantly time-dependent increased blood pressure (Figure 2C) and vascular resistance (Figure 2D). The response to Ach and L-NAME was similar in G3 mice (Figure 2). Similar results were observed when the role of Ang II was tested. The hemodynamic response to both Ang II infusion and Ang II blockade with losartan was comparable in both groups of animals (Figure 3).

The response to ET-1 was different in WT than in G3 mice. Thus, in WT mice, ET-1 induced a sustained increase in MAP as soon as 30 seconds after ET-1 administration. In contrast,
in G3 mice, ET-1 induced a mild transient increase, followed by a maintained decrease in MAP (Figure 4A). After the hind limbs were isolated and perfused, the changes promoted by ET-1 in vascular resistances were similar in WT and G3 animals, with a rapid and transient decrease, followed by a maintained increase in HVR (Figure 4B). Bosentan, a dual ET-A/ET-B receptor antagonist, slightly decreased MAP in WT mice after 10 minutes of administration. This effect was more marked in G3 mice, being detectable after 5 minutes of bosentan treatment (Figure 4C). With respect to the changes in vascular resistance produced by bosentan in isolated perfused hind limbs, it can be seen in Figure 4D that bosentan induced a rapid increase in HVR and a return to normal values that was more rapid and pronounced in G3. G1 mice showed a response to ET-1 and bosentan that was intermediate between WT and G3 animals (Figure 4).

Figure 3. Mice lacking telomerase activity do not show functional modifications in the Ang II system. Changes in MAP (ΔMAP) were recorded in 6 WT (*) and 6 G3 (c) mice treated with Ang II (A) and losartan (C). Isolated HVR was measured under the same conditions (B, D). Results are mean±SEM. Ang II increased MAP and HVR significantly (RMANOVA, P<0.001 in both cases) with no effect of mouse genotype. Losartan decreased MAP (RMANOVA, P<0.005) and HVR (RMANOVA, P<0.001) with no effect of mouse genotype.

Figure 4. Response to ET-1 is impaired in mice lacking telomerase activity. Changes in MAP (ΔMAP) were recorded in 9 WT, 4 G1, and 9 G3 mice treated with ET-1 (A) or bosentan (C). Isolated HVR was measured under the same conditions (B, D). Results are mean±SEM. ET-1 significantly increased MAP in WT but not in G3 mice (RMANOVA, interaction P<0.001). *P<0.05 vs WT at the same time (after Bonferroni correction for pairwise comparisons). ET-1 increased significantly HRV (RMANOVA, P<0.001) with no effect of mouse genotype. Bosentan treatment significantly reduced MAP in G1 and G3 but not in WT mice (RMANOVA, interaction P<0.001). *P<0.05 vs WT at the same time (after Bonferroni correction for pairwise comparisons). Bosentan significantly decreased HVR in G3 mice but not in WT mice (RMANOVA, interaction P<0.001). *P<0.05 vs WT at the same time (after Bonferroni correction for pairwise comparison).
Taking these results together, it can be suggested that increased circulating levels of ET-1 could play a role in the development of hypertension in \( \text{terc}^{-/-} \) animals. To confirm this possibility, ET-1 concentrations were evaluated in plasma and urine from WT, G1, and G3 mice. ET-1 plasma and urine concentrations from \( \text{terc}^{-/-} \) mice were higher than in the WT group (Figure 5A). The source of this ET-1 was indirectly evaluated by studying the pre–pro-ET-1 gene expression in aorta and kidney. No significant differences were found in pre–pro-ET-1 mRNA expression among the 3 experimental groups (Figure 5B and 5C). In contrast, the mRNA expression of ECE-1 was significantly increased in aorta and renal cortex from G1 and G3 mice compared with WT animal (Figure 6A). This result was confirmed by real-time PCR (Figure 6B).

These results point to ECE-1 as being primarily responsible for the increased ET-1 levels detected in telomerase-deficient mice. Treatment of G3 mice with the ECE inhibitor FR901533 caused a fall in AP that was not observed in WT mice (Figure 6C). The maximum effect of FR901533 was obtained after 1 hour of treatment.

The mechanisms involved in ECE-1 upregulation were analyzed by using cultured MEF. ECE-1 protein content was significantly higher in G3 than in WT MEFs (Figure 7A). ECE-1 promoter activity also was increased in these G3 MEFs relative to WT MEFs (Figure 7B). The increased promoter activity detected in G3 MEFs disappeared after incubation of the cells with catalase, NAC, and DPI, suggest-
ing a role for ROS generated by NADPH oxidase in the activation of the ECE-1 promoter. On the other hand, blockade of some kinases such as PI3-kinase, Akt, erk1/2, and JNK also inhibited the activation of the ECE-1 promoter observed in G3 MEFs (Figure 7B). To analyze the transcription factors involved in the ECE-1 promoter activation, MEFs were transfected with the complete ECE-1 promoter and serial deletions mutants, and luciferase activity was measured in basal conditions and after hydrogen peroxide treatment in WT MEFs. Data are mean ± SEM from 5 different experiments. *P<0.05 vs WT transfection with the same promoter construct. CAT indicates catalase; WM, wortmannin (a PI3 kinase inhibitor); Akt inh, Akt inhibitor; PD, PD98059 (an erk1/2 inhibitor); SP, SP 600125 (a JNK inhibitor) (see Methods for details on concentrations).

**Discussion**

Telomere shortening has been proposed as a critical mechanism in aging development, and increased blood pressure is a characteristic feature of the aging process. A link between telomere length and blood pressure has been proposed because hypertensive adult humans present a significant negative correlation between systolic blood pressure and telomere length. Taking all of this information together, it can be proposed that telomere shortening, by inducing changes in the phenotypic expression of vascular cells, could contribute to the development of hypertension. To test this hypothesis, studies in telomerase-deficient mice were performed.

Blood pressure was evaluated by 2 methods. The indirect tail-cuff method, even under the best standardized conditions, induces some degree of stress in animals. Moreover, it does not seem to be the best method to measure diastolic pressure. On the other hand, it is performed in conscious animals without any pharmacological interference. Direct blood pressure measurement, by
invasive methods, provides more precise results, but it requires anesthetizing the animals, which can affect cardiovascular function. This procedure is extremely difficult in G3 animals because of their very low weight and extreme vascular fragility. Usually, direct measurements provide lower blood pressure values than the tail-cuff method, as is the case in our animals. Independently of the method used, telomerase-deficient animals were shown to be hypertensive.

Different mechanisms could explain the development of increased blood pressure in the telomerase-deficient mice. Vascular cell senescence has been related to vascular aging and cardiovascular diseases such as atherosclerosis, hypertension, and diabetes. 

Endothelial dysfunction has been described that NO production is impaired in senescent endothelial cells but is restored on transfection with the catalytic subunit of telomerase, our results do not support this theory.

For these reasons, we tested the role of endothelial vasoactive factors, particularly NO and ET, in the genesis of the G3 mouse hypertension. Additionally, the role of Ang II was tested.

Hemodynamic studies have been proved useful for assessing the role of these factors. Measuring blood pressure or vascular resistances in the presence of their agonists or antagonists provides valuable information about their pathogenic significance. Ach and L-NAME were used to modulate NO synthesis, and Ang II and losartan were used to explore the importance of the renin-angiotensin system. In these assays, no differences were detected between WT and G3 mice. Although it has been described that NO production is impaired in senescent endothelial cells but is restored on transfection with the catalytic subunit of telomerase, our results do not support this role either for NO or Ang II in the genesis of hypertension in telomerase-deficient mice.

The results obtained on exogenous ET-1 and bosentan administration point to the presence of high levels of circulating ET-1 in G1 and G3 mice, because minor changes in blood pressure after exogenous ET-1 administration and an increased response to bosentan were observed in these animals. Experiments in isolated hind limbs were performed to complete the analysis of vasoactive responses without interferences resulting from compensatory heart responses. The results must be interpreted taking into account the facts that the hindlimb vascular beds were washed before the experiments was started and that the perfusion fluid did not contain ET-1 except when it was incorporated into it. In all groups of animals, HVR increased in response to exogenous ET-1. This excludes a possible defective vascular vasoconstriction or a lack of ET-1 receptors in G1 and G3 animals. Moreover, the results with bosentan suggest that the vascular beds could be the source of the increased ET-1, at least partially, in the telomerase-deficient mice. This drug increased HVR in both groups of animals, perhaps as a consequence of the blockade of the ET-1 receptor B. However, it decreased vascular resistance only in G3 mice, suggesting an ET-1 overproduction in the vessel walls of these animals.

To further confirm the role of ET-1, serum and urine concentrations were measured. G1 and G3 mice showed higher levels of ET-1 in serum and urine than WT mice. Increased ET-1 levels have been found in plasma and tissues of patients with cardiovascular diseases, atherosclerosis, myocardial infarction, pulmonary hypertension, heart failure, and renal failure. Such changes may reflect increased production and/or reduced metabolism of ET-1.

We did not detect any difference in the mRNA expression levels of pre–pro-ET-1 in aorta and renal cortex between the telomerase-deficient and WT mice. Because synthesis of bioactive ET-1 requires ECE-1, we measured ECE-1 gene expression in the aorta and renal cortex of mice. ECE-1 mRNA expression was significantly higher in G1 and G3 than in WT mice. Therefore, we can speculate that the increased levels of circulating ET-1 may be due to increased expression of ECE-1. Elevated ECE-1 mRNA levels have been found in the kidneys of spontaneously hypertensive rats, and it has been proposed that ECE-1 could contribute to the development and maintenance of the elevated blood pressure through an increase in ET-1 production. In our model, FR901533, an ECE inhibitor at least 3 times more potent than phosphoramidon, decreased AP only in the telomerase-deficient group, stressing the importance of this mechanism in the hypertension of these animals.

The mechanisms responsible for the ECE-1 upregulation have been studied in MEFs because fibroblasts synthesize ECE-1. Significantly increased amounts of this protein and an activation of the ECE-1 promoter were detected in MEFs from G3 mice, suggesting that changes in the transcriptional activity of the ECE-1 gene could be responsible for the changes in ECE-1 content. Because ROS increases ECE-1 promoter activity in bovine aortic endothelial cells, we tested the hypothesis that ROS also could be responsible for the changes observed in MEFs. G3 MEFs showed an increased synthesis of ROS, and the augmented ECE-1 promoter activity detected in these cells disappeared in the presence of catalase and NAC. This fact supports a role for ROS in the upregulation of the ECE-1 gene in G3 MEF. NADPH oxidase seems to be the main source of ROS because DPI, an inhibitor of this enzyme, blocked the increased ROS synthesis detected in G3 MEFs, an effect that was not observed with the different kinase inhibitors selected. The importance of NADPH oxidase activation in the genesis of these effects was further confirmed by measuring ECE-1 promoter activity in the presence of DPI. The enzyme inhibitor blocked the promoter activation observed in G3 MEFs.

Some of the pathways involved in the ECE-1 promoter activation in MEF from G3 mice also were studied. Intracellular kinases such as PI3-kinase, AKT, and erk1/2 could be responsible for the promoter upregulation because pharmacological inhibitors of these kinases prevented the promoter activation in G3 MEFs. Moreover, transfection experiments with serial deletions of this promoter pointed to AP-1 as one of the possible transcription factors involved in the ROS-dependent ECE-1 promoter upregulation. Experiments with a rather specific JNK inhibitor stressed this possibility.

The present results demonstrate the existence of a direct link between telomerase deficiency and hypertension. In
fact, telomerase-deficient mice show higher blood pressure than WT mice. Evidence also is presented that points to ECE-1 as one of the factors responsible for the high blood pressure. However, additional mechanisms could be involved to adequately explain the differences in blood pressure observed between G1 and G3 mice. Telomerase activity and ECE-1 content are similar in these animals, but they differ in telomere length32 and blood pressure levels. With this evidence, we can speculate that telomerase deficiency and telomere shortening may induce changes in the phenotypic expression of vascular cells, particularly, but not only, ECE-1 overexpression, with subsequently increased levels of circulating ET-1 and development of hypertension.

Considering the MEF experiments, a hypothesis that explains the cellular mechanisms involved in the ECE-1 overexpression may be proposed. Telomerase-deficient cells show an activation of NADPH oxidase that leads to increased ROS synthesis. ROS could activate some intracellular kinases, particularly PI3-kinase, Akt, and erk1/2, and then the transcription factor AP-1. As a consequence, the ECE-1 promoter activity increases, with a subsequent increase in protein content. However, additional experiments are needed to explore these pathways in more detail.

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**Disclosures**

None.

**References**


Hypertension is the most prevalent disease in elderly individuals. Although some drugs have been proposed as being especially effective in the treatment of these patients, no particular antihypertensive drug has been proved more useful in this age group. The analysis of specific mechanisms particularly involved in the development of age-related hypertension could provide valuable information for a rational approach to the treatment of this disorder. The present study suggests a pivotal role for ECE-1 in the genesis of hypertension in an experimental model of premature aging (telomerase-deficient mice). Moreover, the results support a link between redox imbalance and the observed changes in endothelin-converting enzyme. This information could constitute the basis for future treatments of hypertension in elderly people.
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