Targeted Deletion of Nuclear Factor κB p50 Enhances Cardiac Remodeling and Dysfunction Following Myocardial Infarction

Leo Timmers,* J. Karlijn van Keulen,* Imo E. Hoefer, Matthijs F.L. Meijs, Ben van Middelaar, Krista den Ouden, Cees J.A. van Echteld, Gerard Pasterkamp, Dominique P.V. de Kleijn

Abstract—Myocardial infarction is commonly complicated by left ventricular remodeling, a process that leads to cardiac dilatation, congestive heart failure and death. The innate immune system plays a pivotal role in the remodeling process via nuclear factor (NF)-κB activation. The NF-κB transcription factor family includes several subunits (p50, p52, p65, c-Rel, and Rel B) that respond to myocardial ischemia. The function of NF-κB p50, however, is controversial in this process. To clarify the role of NF-κB p50 in postinfarct left ventricular remodeling, myocardial infarction was induced in wild-type 129Bl6 mice and NF-κB p50–deficient mice. Without affecting infarct size, deletion of NF-κB p50 markedly increased the extent of expansive remodeling (end-diastolic volume: 176±13 μL versus 107±11 μL; P=0.003) and aggravated systolic dysfunction (left ventricular ejection fraction: 16.1±1.5% versus 24.7±3.7%; P=0.029) in a 28-day time period. Interstitial fibrosis and hypertrophy in the noninfarcted myocardium was increased in NF-κB p50 knockout mice. In the infarct area, a lower collagen density was observed, which was accompanied by an increased number of macrophages, higher gelatinase activity and increased inflammatory cytokine expression. In conclusion, targeted deletion of NF-κB p50 results in enhanced cardiac remodeling and functional deterioration following myocardial infarction by increasing matrix remodeling and inflammation. (Circ Res. 2009;104:699-706.)

Key Words: myocardial infarction ■ ischemic heart disease ■ remodeling ■ NF-κB ■ wound healing

Myocardial infarction (MI) is commonly complicated by maladaptive left ventricular (LV) remodeling, which refers to alterations in LV chamber mass, geometry, and function.1 Remodeling is a chronic process, mediated by progressive structural changes in cardiomyocytes and the extracellular matrix (ECM), leading to LV dilatation and impaired systolic function, and potentiates the development of ventricular arrhythmias, heart failure, and subsequent cardiovascular mortality.2-4 Recently, we have shown that deletion of Toll-like receptor 4 limits ventricular remodeling and improves cardiac function after MI, identifying the innate immune system as a major player in the remodeling process via nuclear factor (NF)-κB activation. The NF-κB–dependent transcription of a large and diverse array of target genes that modulate various physiological and pathological processes, including MI.

Following MI, activation of NF-κB mediates maladaptive LV remodeling and functional deterioration.10 Blocking of NF-κB activity was therefore suggested to be a promising novel approach to prevent adverse LV remodeling following MI. The role of the different NF-κB subunits following MI, however, has not been completely clarified thus far. In this study, we investigate the role of the NF-κB p50 subunit in LV remodeling, myocardial infarction was induced in wild-type 129Bl6 mice and NF-κB p50–deficient mice. Without affecting infarct size, deletion of NF-κB p50 markedly increased the extent of expansive remodeling (end-diastolic volume: 176±13 μL versus 107±11 μL; P=0.003) and aggravated systolic dysfunction (left ventricular ejection fraction: 16.1±1.5% versus 24.7±3.7%; P=0.029) in a 28-day time period. Interstitial fibrosis and hypertrophy in the noninfarcted myocardium was increased in NF-κB p50 knockout mice. In the infarct area, a lower collagen density was observed, which was accompanied by an increased number of macrophages, higher gelatinase activity and increased inflammatory cytokine expression. In conclusion, targeted deletion of NF-κB p50 results in enhanced cardiac remodeling and functional deterioration following myocardial infarction by increasing matrix remodeling and inflammation. (Circ Res. 2009;104:699-706.)

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remodeling and cardiac dysfunction following MI. NF-κB p50 is generally considered to be an inhibitory subunit of the NF-κB complex. We therefore hypothesize that targeted deletion of NF-κB p50 will enhance NF-κB mediated inflammation, cardiac remodeling and functional deterioration following MI.

Materials and Methods

Nuclear Expression of p65 and Interleukin-6 Cytokine Blotting

Mouse embryonic fibroblasts were cultured in DMEM (Invitrogen) with MEM nonessential amino acids 1× (Invitrogen), 50 μg/mL 2-mercaptoethanol (Sigma), 100 U/mL penicillin, 100 μg/mL streptomycin (Gibco), and 10% FBS (Gibco). P3-4 cells stained in 0.1% FBS were stimulated with 100 ng/mL lipopolysaccharide (LPS). Nuclear proteins were isolated using the Nuclear Extract Kit (Active Motive, 40010). Subsequently, translocation of p65 after stimulation with LPS was measured with the TransAM NF-κB Family kit (Active Motif, 43296). Medium was collected 24 hours after LPS stimulation. Medium of 4 different wells was pooled and used for interleukin (IL)-6 cytokine blotting. This assay was performed according to the protocol of the manufacturer (RayBiotech, Norcross, Ga).

Animals

All experiments on 46 NF-κB knockout (KO) mice on a 129B6 background (Harlan, Indianapolis, Ind) and 46 wild-type mice (129B6, Harlan) were performed in accordance with the Guide for the Care and Use of Laboratory Animals prepared by the Institute of Laboratory Animal Resources and with prior approval by the Animal Experimentation Committee of the Faculty of Medicine, Utrecht University, The Netherlands. Mice were used for the following purposes: 10 NF-κB KO mice and 10 129B6 mice for serial MRI, collagen, and hypertrophy quantification at 28 days post-MI; 10 NF-κB KO mice and 10 129B6 mice for histology 7 days post-MI; 10 NF-κB KO mice and 10 129B6 mice for TRIS protein isolation 7 days post-MI; and 16 NF-κB KO mice and 16 129B6 mice for tripeptide protein isolation 7 days post-MI.

Surgical Protocol: Myocardial Infarction

Mice (all male and 10 to 12 weeks old) were anesthetized with isoflurane and intubated using a 20-gauge intravenous catheter with a blunt end. Mice were artificially ventilated at a rate of 150 strokes per minute using a rodent ventilator with a mixture of O₂ and air (1:2 vol/vol) to which isoflurane (1.8 to 2.1% vol/vol) was added. The mouse was placed on a heating pad to maintain the body temperature at 37°C. The chest hair was removed using hair removal cream. The chest was opened in the third intercostal space and an 8-0 Prolene suture was used to permanently ligate the left coronary artery. The chest was closed and the animals were extubated before they were allowed to recover from the surgery.

Magnetic Resonance Imaging

For a description of the MRI measurements, refer to the expanded Materials and Methods section in the online data supplement, available at http://circres.ahajournals.org.

Histology, Collagen Density, and Myocyte Cross-Sectional Area

Seven days (for MAC-3) or 28 days (for Picrosirius red and hematoxylin/eosin), following MI, the hearts were excised for histological analysis. Quantification of collagen density was performed after 28 days using Picrosirius red staining with circularly polarized light and digital image microscopy after conversion into grey value images, as described before. A hematoxylin/eosin staining was performed to delineate the cardiomyocytes. Four randomly picked fields within the remote area were selected and the myocyte cross-sectional area was measured by computer-based planimetry (Analysis, Soft Imaging System, Münster, Germany), averaged across the 4 fields, and expressed as the mean area per cardiomyocyte. MAC-3 staining was performed for visualization of macrophages. For a more detailed description of histological methods, refer to the online data supplement.

Matrix Metalloproteinase Activity Assays and TIMP-2 ELISA

Heart tissue samples were harvested from infarct area and remote area 7 days following MI for assessment of markers of matrix turnover. Matrix metalloproteinases (MMP)-2 and MMP-9 activity assays and TIMP-2 ELISA were performed using undiluted protein according to the instructions of the manufacturers (Amersham, Munich, Germany [MMP assays] and GE Healthcare, Buckinghamshire, UK [TIMP-2 ELISA]), and the results were corrected for sample protein concentration. For more detailed information, refer to the online data supplement.

Polymerase Chain Reaction

Total RNA was extracted from injured and remote myocardium, 7 days after MI, using TriPure reagent (Roche) according to the instructions of the manufacturer. RNA was reverse transcribed into cDNA. One microgram of second-strand cDNA was used as a template for quantitative RT-PCR, as described previously, using the following oligonucleotide primers: transforming growth factor (TGF)-β1 (Superarray Biosciences Corp, Frederick, Md), procollagen I (forward: 5′-ctcaaggtctagctcaagctgg-3′; reverse: 5′-aatcatggcatctgctct-3′), monocyte chemoattractant protein-1 (forward: 5′-gatgcaacagatgtagacg-3′; reverse: 5′-gtggaaagagtggtgatc-3′), intercellular adhesion molecule-1 (Superarray), and vascular cell adhesion molecule-1 (Superarray). All mRNA expression levels were normalized to calsemin mRNA (forward: 5′-ccagcattctctctc-3′; reverse: 5′-ttccttcatctactc-3′) and expressed as a ratio.

Flow Cytometric Cytokine Measurement

Tumor necrosis factor (TNF)-α, IL-6, and IL-10 expression were measured in TriPure (Roche) isolated protein samples harvested 7 days after MI using the Th1/Th2 kit (Bender MedSystems, Vienna, Austria). The protein samples were diluted 1:1 in assay buffer, and the protocol was further followed according to the instructions of the manufacturer.

Bone Marrow Transplantation

Bone marrow transplantations were performed in a crossover design. At the age of 6 weeks, mice were irradiated at a dose of 700 cGray (1030 monitor units) before bone marrow transplantation. Bone marrow was isolated from 4 donor mice by flushing the femoral and the humeral bone with RPMI 1640 medium (Invitrogen). Each mouse received 4.5 million cells via the tail vein. The animals were allowed to recover for 6 weeks before MI was induced. Of each strain, n=8 animals were subjected to allogeneic bone marrow transplantation (NF-κB p50 KO→129B6).

Data Analysis

The data were collected and analyzed in a blinded fashion. Data are presented as means±SE. Mortality between NF-κB KO mice and 129B6 mice was compared using Fisher’s exact test. Myocardial infarct size and nuclear expression of p65 with and without LPS stimulation were compared using Students t test. Functional data were compared using a 2-way ANOVA for repeated measures and Bonferroni post hoc tests. Expression levels and histological data were statistically analyzed using a 1-way ANOVA and Bonferroni post hoc tests. Probability values of <0.05 were considered significant.
MEFs of 129Bl6 mice 1 hour following PBS stimulation (C) and 1 hour following LPS stimulation (D) and of NF-κB–deficient MEFs from NF-κB p50 KO mice 1 hour following PBS stimulation (E) and 1 hour following LPS stimulation (F). ‡P<0.01 compared to baseline value, §P<0.01 compared to wild type.

Results
Nuclear Expression of NF-κB p65 Occurs in NF-κB p50–Deficient Mice and Increases on Stimulation
Following extraction of nuclear proteins from mouse embryonic fibroblasts (MEFs) of NF-κB p50 KO mice, we found NF-κB p65 to be expressed in the nuclei. Following stimulation with LPS, nuclear translocation of NF-κB p65 increased, showing that nuclear translocation of NF-κB occurs following stimulation in NF-κB p50 KO cells (Figure 1A and 1C through 1F).

NF-κB p50 Deficiency Increases Secretion of IL-6 In Vitro
To assess the inflammatory response of cells lacking the NF-κB p50 subunit, the secretion of IL-6 by mouse embryonic fibroblasts of 129Bl6 mice and NF-κB p50 KO mice was measured following LPS stimulation. Production of IL-6 was higher following LPS stimulation in NF-κB p50 KO cells compared to wild-type cells, pointing to an inhibitory role of NF-κB p50 in inflammation (Figure 1B).

Mortality
Seven NF-κB KO mice and 4 129Bl6 mice died within 24 hours following MI without signs of cardiac rupture, probably attributable to fatal arrhythmias and were therefore excluded from the study. There was no significant difference on mortality between NF-κB KO mice and 10 129Bl6 mice (15% versus 9%, respectively; P=0.261).

Targeted Deletion of the NF-κB p50 Subunit Enhances LV Remodeling and Functional Deterioration Following Myocardial Infarction
Before induction of MI, LV geometry and function did not differ between NF-κB p50 KO mice and 129Bl6 mice. Coronary artery ligation resulted in expansive LV remodeling and functional impairment in all mice, whereas in sham operated animals such changes were not observed. The increase in LV end-diastolic volume (EDV) and end-systolic volume (ESV) was significantly more pronounced in NF-κB p50 KO mice compared to 129Bl6 mice (Figure 2A and Table 1). Whereas LV volumes were similar at 4 days following coronary artery ligation, a striking difference became apparent 28 days following coronary artery ligation. Increased LV remodeling in NF-κB p50 KO mice was accompanied by enhanced functional deterioration, as became evident from significantly lower LV ejection fractions (Figure 2B). LV mass increased in NF-κB p50 KO mice, in contrast to 129Bl6 mice, pointing to hypertrophic changes in the remote myocardium. In NF-κB p50 KO mice, remodeling was more pronounced in both infarct and remote myocardium. The inner perimeter of the infarct increased from 4.88±0.16 mm (4 days) to 9.21±0.82 mm (28 days) in NF-κB p50 KO.
mice and from 4.28±0.16 mm (4 days) to 5.46±0.35 mm (28 days) in 129Bl6 mice (relative increase 84.5±9.3% versus 31.3±4.8%; P=0.001). The inner perimeter of the remote myocardium increased from 9.55±0.25 mm (4 days) to 12.49±0.66 mm (28 days) in NF-κB p50 KO mice and from 8.90±0.32 mm (4 days) to 10.06±0.40 mm (28 days) in 129Bl6 mice (relative increase 30.0±3.6% versus 13.0±1.3%; P=0.003). All functional parameters are presented in Table 1.

Initial myocardial injury was not affected by deletion of NF-κB p50 as infarct size did not differ at 4 days post MI (41.2±3.8% of the LV [129Bl6] versus 41.8±3.2% of the LV [NF-κB p50 KO]; P=0.915). Infarct size after 28 days however was smaller in NF-κB p50 KO mice (30.7±1.8% versus 39.7±3.8% of the LV; P=0.036). Representative pictures of MR images are shown in Figure 3.

The Inflammatory Response Following Myocardial Ischemic Injury Is Increased in NF-κB p50–Deficient Mice

Both border areas and infarct areas of NF-κB p50 KO mice contained more macrophages compared to 129Bl6 mice (12.8±1.0 versus 7.3±1.0 macrophages/mm² [P=0.002] and 38.7±2.4 versus 22.9±3.2 macrophages/mm² [P=0.005], respectively; Figure I in the online data supplement). In the remote area, macrophages were detected sporadically and no differences were observed between NF-κB p50 KO mice and 129Bl6 mice. Gene expression of the adhesion molecule vascular cell adhesion molecule-1 was increased in myocardial infarct tissue compared to noninfarcted tissue (Table 2); however, no differences between both mouse types were detected. Gene expression of monocyte chemoattractant protein-1, on the other hand, was higher in infarcts of NF-κB p50 KO mice compared to 129Bl6 mice. In addition, expression analysis of the proinflammatory cytokines TNF-α and IL-6 and the antiinflammatory cytokine IL-10 was performed on the protein level. TNF-α and IL-6 expression was higher in infarct tissue of NF-κB p50 KO mice compared to 129Bl6 mice, whereas IL-10 expression was lower (Table 2).

NF-κB p50 Modulates ECM Turnover and Myocardial Hypertrophy

Collagen density was increased in myocardial infarct tissue compared to baseline values (Figure 4A through 4E). In infarcts of NF-κB p50 KO mice, however, collagen density was significantly lower compared to 129Bl6 mice. Gene expression of procollagen 1 and the profibrotic factor TGF-β1 in the infarct area did not differ between both mouse types, providing no evidence for decreased collagen production. Gelatinase activity by MMP-2 and MMP-9, however, were increased in NF-κB p50 KO mice compared to 129Bl6 mice, indicating that ECM degradation was increased in these mice. TIMP-2 expression did not differ between the mouse strains. All expression data are presented in Table 2.

In the remote area of 129Bl6 mice, no changes in collagen density were observed compared to baseline. In NF-κB p50 KO mice, however, a small but significant increase became apparent, suggesting the occurrence of interstitial myocardial fibrosis. Gene expression of procollagen 1 and TGF-β1 was increased in remote areas of NF-κB p50 KO mice compared to 129Bl6 mice. Also the myocardial hypertrophic response in NF-κB p50 KO mice was enhanced compared to wild-type mice, as became apparent from quantification of the myocyte cross-sectional area (Figure 4F).

Lack of NF-κB p50 in Circulating Cells and Cardiac Remodeling Following Myocardial Infarction

Cardiac remodeling and functional deterioration was more pronounced in 129Bl6 mice that received NF-κB p50 KO bone marrow compared to NF-κB p50 KO mice that received 129Bl6 bone marrow (EDV, 167±9.4 versus 110±6.1 μL [P=0.005]; EF, 17.6±1.7 versus 26.4±2.1% [P=0.007]). There were no differences between 129Bl6 mice that received

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Cardiac functional parameters of 129Bl6 mice and NF-κB p50 KO mice measured before induction of MI (baseline) and 28 days after MI (MI). EF indicates ejection fraction; WT, wall thickness; SWT, systolic wall thickening. Perimeters and perimeters and infarct refer to the percentage increase of the inner perimeter of the remote area and infarct area respectively, between 4 days and 28 days post-MI. 129Bl6, n=8; NF-κB p50 KO, n=9. *P<0.05; §P<0.01 compared to 129Bl6; ‡P<0.01 compared to baseline.
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NF-κB p50 KO bone marrow and NF-κB p50 KO mice (EDV, 167±9.4 versus 176±13.3 μL [P=1.000]; EF, 17.6±1.7 versus 16.1±1.5% [P=1.000]) or between NF-κB p50 KO mice that received 129B16 bone marrow and 129B16 mice (EDV, 110±6.1 versus 107±10.9 μL [P=1.000]; EF, 26.4±2.1 versus 24.7±3.7% [P=1.000]).

Discussion

Thus far, the role of NF-κB in MI healing remains controversial. Several studies have identified NF-κB as a mediator of the inflammatory response to myocardial ischemia. Toll-like receptors, which signal through NF-κB, have been demonstrated to play a pivotal role in post MI left ventricular remodeling.5,16 Blockade of NF-κB by the introduction of double-stranded decoy DNA with high affinity for NF-κB reduced myocardial ischemia and reperfusion injury in a rat model.9 A similar effect of NF-κB blockade was observed in a mouse model of ischemia and reperfusion injury.17 In a mouse model of permanent coronary artery ligation, however, NF-κB blockade increased infarct size, suggesting that NF-κB can exert cytoprotective effects.18 Also in left ventricular remodeling and heart failure progression following MI, a mediating role of NF-κB has been reported. LV remodeling and cardiac dysfunction can be ameliorated by using a phosphorylation inhibitor of IκB to inhibit NF-κB nuclear translocation.10 Blocking of NF-κB activity was therefore suggested to be a promising novel approach to prevent adverse LV remodeling following MI. However, a more detailed understanding of NF-κB function, in particular, of the specific function of the different subunits, is required. In this study, we focused on the function of NF-κB p50 following MI. The p50 subunit is generally considered to be an inhibitory subunit of the NF-κB complex.11-13 Because p50/p50 homodimers have indeed been shown to inhibit transcriptional activity, we hypothesized that targeted deletion of NF-κB p50 will enhance cardiac remodeling and functional deterioration following MI. In contrast, previously published studies reported that p50 KO mice were protected against LV remodeling following MI, which was assessed using short axis echocardiography.19-21 In the present study, however, we provide evidence for a protective role of NF-κB p50 following MI using high resolution MRI (9.4 Tesla), which provides a more accurate means of measuring cardiac geometry and offers 3D quantification versus 2D quantification with short-axis echocardiography. Our data demonstrated that targeted deletion of NF-κB p50 markedly enhances maladaptive LV remodeling and functional deterioration following coronary artery ligation.

In the present study, NF-κB p50 deletion did not influence the initial myocardial injury because myocardial infarct size was comparable after 4 days. This is attributable to the permanent nature of coronary artery ligation, and, therefore, this model was used to assess the influence of NF-κB p50 on LV remodeling and heart failure development via other mechanisms than by reducing cardiomyocytes death. Targeted deletion of NF-κB p50 resulted in markedly enhanced expansive LV remodeling, both of infarct and remote area and functional impairment. EDV and ESV were markedly higher in NF-κB p50 mice. Twenty-eight days after MI, the infarct area of NF-κB p50 mice was smaller but more expanded and thinner compared to 129B16 mice, making it more susceptible to the impact of mechanical loading forces that drive the remodeling process. In addition, NF-κB p50 deletion resulted in increased LV mass and increased cardiomyocyte hypertrophy. Whereas differences in cardiac functional parameters between NF-κB p50 KO mice and 129B16 mice were not apparent 4 days after coronary artery ligation, the differences at 28 days were remarkable. This suggests that NF-κB p50 has as protective effect on late maladaptive LV remodeling following MI.
Several mechanisms may have contributed to enhanced LV remodeling in NF-κB p50 KO mice. First, ECM turnover plays an important role in LV remodeling following MI. Various members of the MMP family have been described to mediate post-MI LV remodeling.\textsuperscript{22–24} Specifically MMP-9 is recognized as a major contributor. Targeted deletion of MMP-9 results in significantly reduced LV enlargement following MI.\textsuperscript{25} In our study, gelatinase activity by MMP-9 was significantly higher in remote areas and infarct areas of NF-κB p50 KO mice compared to 129Bl6 mice. Also MMP-2 activity was higher in infarct areas of NF-κB p50 KO mice, whereas no difference was found in TIMP-2 levels between 129Bl6 and NF-κB p50 KO mice. This may explain the reduced collagen density observed in the myocardial infarct area and enhanced LV remodeling of both infarct area and remote area in NF-κB p50 KO mice. A reduction in collagen density decreases the tensile strength of the MI. We cannot exclude, however, that remodeling of the remote myocardium was secondary to increased infarct expansion, which lead to increased pressure and volume overload in the ventricle.

In the remote area, collagen density was higher in NF-κB p50 KO mice compared to 129Bl6 mice, pointing to interstitial myocardial fibrosis, which is commonly observed in heart failure. ECM turnover is a complicated process, in which a balance between degradation (by MMPs) and synthesis of ECM molecules determines the density of the matrix. We have also assessed gene expression of procollagen 1 and the profibrotic growth factor TGF-β\textsubscript{1} to find a mechanistic explanation for increased collagen synthesis. Procollagen 1 and TGF-β\textsubscript{1} gene expression was higher in remote areas of NF-κB p50 KO mice compared to 129Bl6 mice. This may explain increased myocardial fibrosis in the remote myocardium of NF-κB p50 KO mice despite higher MMP-9 activity.

Besides matrix turnover, inflammatory mediators are involved in LV remodeling. An in vitro assay revealed that the production and secretion of IL-6 increased in stimulated embryonic fibroblasts isolated from NF-κB p50 KO mice compared to those isolated from 129Bl6 mice. Expression of IL-6 was also increased in vivo following MI, as was TNF-α. Accordingly, the influx of monocytes to the infarct area of NF-κB p50 KO mice was increased compared to 129Bl6 mice. On the other hand, expression of the antiinflammatory cytokine IL-10 was decreased. NF-κB p50 has been described to bind to the IL-10 promoter and to increase IL-10 production in macrophages.\textsuperscript{26} Inflammatory cytokines have been demonstrated to be involved in ischemic injury by enhancing oxidative stress, whereas IL-10 mitigates oxidative stress.\textsuperscript{27} Sustained presence of TNF-α leads to myocyte phenotype transition and activation of MMPs, augmenting the remodeling process.\textsuperscript{28}

Also in other studies, increased expression of inflammatory cytokines was observed in NF-κB p50 KO mice following MI.\textsuperscript{19,20} Paradoxically, these studies reported that NF-κB translocation was blocked in NF-κB p50 KO mice, which resulted in reduced remodeling and heart failure progression, which was measured using short axis echocardiography. We have found, however, that p65 is expressed in nuclei of NF-κB p50 KO cells and that nuclear p65 expression increases following LPS stimulation. This demonstrates that nuclear translocation of subunits other than p50 occurs on stimulation in the absence of p50. When p50 is lacking, the remaining subunits form alternative homo- or heterodimers (eg, p65-p65) to regulate gene expression. Deletion of NF-κB p50 can therefore not be simply considered as NF-κB blockade. In contrast, NF-κB p50 is an inhibitory subunit that controls the inflammatory response and ECM degradation. Whereas deletion of TLR4 (ie, indirect inhibition of NF-κB)
reduces inflammation and cardiac remodeling following MI. Deletion of p50 enhances these processes. The extent of NF-κB mediated inflammation may therefore be a key determinant of postinfarction LV remodeling.

Bone marrow transplantations revealed that circulating cells lacking NF-κB p50, rather than local cardiac factors, are responsible for the effect on cardiac remodeling, because irradiated wild-type 129B16 mice with NF-κB p50 KO bone marrow demonstrated a remodeling response that was similar to NF-κB p50 mice. Conversely, NF-κB p50 KO mice with wild-type bone marrow demonstrated a remodeling response that was comparable to wild-type mice.

In summary, nuclear expression studies and cytokine expression data suggest that NF-κB p50 deficiency does not block NF-κB signaling. In contrast, NF-κB p50 is an important regulator of the inflammatory response and ECM matrix turnover following MI, and targeted deletion of NF-κB p50 results in markedly enhanced LV remodeling and functional deterioration. These data provide an important contribution to the basic understanding of the function of NF-κB, and the innate immune system in general, in myocardial infarct healing.

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Disclosures
None.

References


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Figure 1