Heart Failure

Biglycan Is Required for Adaptive Remodeling After Myocardial Infarction

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Background—After myocardial infarction (MI), extensive remodeling of extracellular matrix contributes to scar formation and preservation of hemodynamic function. On the other hand, adverse and excessive extracellular matrix remodeling leads to fibrosis and impaired function. The present study investigates the role of the small leucine-rich proteoglycan biglycan during cardiac extracellular matrix remodeling and cardiac hemodynamics after MI.

Methods and Results—Experimental MI was induced in wild-type (WT) and bgn−/− mice by permanent ligation of the left anterior descending coronary artery. Biglycan expression was strongly increased at 3, 7, and 14 days after MI in WT mice. bgn−/− mice showed increased mortality rates after MI as a result of frequent left ventricular (LV) ruptures. Furthermore, tensile strength of the LV derived from bgn−/− mice 21 days after MI was reduced as measured ex vivo. Collagen matrix organization was severely impaired in bgn−/− mice, as shown by birefringence analysis of Sirius red staining and electron microscopy of collagen fibrils. At 21 days after MI, LV hemodynamic parameters were assessed by pressure-volume measurements in vivo to obtain LV end-diastolic pressure, end-diastolic volume, and end-systolic volume. bgn−/− mice were characterized by aggravated LV dilation evidenced by increased LV end-diastolic volume (bgn−/−, 111±4.2 μL versus WT, 96±4.4 μL; P<0.05) and LV end-diastolic pressure (bgn−/−, 24±2.7 versus WT, 18±1.8 mm Hg; P<0.05) and severely impaired LV function (EF, bgn−/−, 12±2% versus WT, 21±4%; P<0.05) 21 days after MI.

Conclusion—Biglycan is required for stable collagen matrix formation of infarct scars and for preservation of cardiac hemodynamic function. (Circulation. 2008;117:1269-1276.)

Key Words: collagen • myocardial infarction • extracellular matrix • fibrosis • proteoglycans

Extensive remodeling of the extracellular matrix (ECM) occurs during all phases of infarct healing, including initial degradation of ECM by matrix metalloproteinases (MMPs), the formation of provisional ECM by de novo synthesis, and finally the deposition of collagen-forming scar tissue.1 During scar maturation, inflammatory cells and fibroblasts disappear as a result of apoptosis, and collagen becomes increasingly crosslinked to stabilize the scar and to provide tensile strength until a hypocellular, collagen-rich scar is formed.2 The composition of the ECM during the individual phases of infarct healing not only determines the mechanical stability but also modulates the cellular phenotype.3 In the long term, adverse left ventricular (LV) remodeling, including fibrosis and ventricular dilatation, often causes progressive heart failure associated with considerable morbidity and mortality after acute myocardial infarction (MI).

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The role of MMPs during postinfarct remodeling has been studied extensively. After MI, an imbalance between MMPs

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and tissue inhibitors of MMPs (TIMPs) is thought to be a key factor in promoting adverse remodeling of the ECM and LV dilatation. However, collagen synthesis and fibrillogenesis also underlie a complex regulation and might in turn be equally important during infarct healing. Self-assembly of procollagen α chains forms triple-helical collagen molecules that associate into collagen fibrils. This process is regulated by accessory ECM molecules such as the family of small leucine-rich proteoglycans, including biglycan and decorin.4 By controlling lateral assembly of triple helices into fibrils and the arrangement of collagen fibers, biglycan and decorin are key regulators of collagen fibrillogenesis and fibril diameter.4,5 Biglycan and decorin are capable of specific binding to collagen types I, II, III, and VI6,7 via the core proteins near the d band of collagen fibrils.8,9 The role of small leucine-rich proteoglycans in LV remodeling is only partially understood. It has been reported previously that biglycan and decorin are induced after MI in rats and that biglycan associates with cardiac fibroblasts in the infarcted myocardium.10,11 bgn−/− mice have reduced skeletal growth and develop an osteoporosis-like phenotype resulting from a defect in bone formation.12 Furthermore, the diameter of collagen fibrils was reduced in bgn−/− mice.13 Other functions of biglycan include regulation of transforming growth factor β-1 activity,14 cell proliferation, apoptosis,15 and activation of inflammatory responses mediated through activation of Toll-like receptor-2 and -4.16 Taken together, biglycan plays important roles in collagen matrix assembly, control of growth factor activity, and cellular phenotype, including inflammatory cells. However, it is still unknown whether biglycan plays a role in cardiac physiology or during infarct healing. The aim of the present study was to investigate the role of biglycan during remodeling and functional adaptation after experimental MI. For this purpose, bgn−/− mice were subjected to permanent occlusion of the left anterior descending coronary artery, followed by analysis of heart morphology, ECM, and hemodynamic function.

Methods

A detailed description of the methods and materials is available in the online Data Supplement.

Animals

bgn−/− mice (bred at the University of Düsseldorf) with a targeted deletion of the bgn gene12 and male wild-type (WT; C57BL/6) littermates were compared in this study. All procedures were carried out in accordance with the Association for Assessment and Accreditation of Laboratory Animal Care guidelines and the Guide for the Care and Use of Laboratory Animals (Department of Health and Human Services, National Institutes of Health, publication No. 86-23) and were approved by the ethics and research boards of the University of Düsseldorf. Animals (12 to 16 weeks old) were randomized as indicated.

Myocardial Infarction

At the age of 12 weeks, WT and bgn−/− mice were anesthetized by injection of pentobarbital (100 mg/kg IP). Mice were subjected to permanent left anterior descending coronary artery occlusion, followed by recovery for 7 or 21 days. All procedures were carried out as recently described in detail.17

Hemodynamic Measurements

Mice were anesthetized by injection of thiopental (125 mg/kg IP), intubated, and ventilated with a respirator (type 7025, Ugo Basile, Comerio, Italy). A 1.4F microconductance pressure catheter (ARIA SPR-719, Millar Instruments Inc, Houston, Tex) was positioned in the LV via the right carotid artery for continuous registration of LV pressure-volume loops in closed-chest animals.18 Systolic function and myocardial contractility were quantified by LV end-systolic pressure, peak rate of rise in LV pressure (dP/dtmax), ejection fraction, cardiac output, end-systolic volume, and stroke volume. Diastolic performance was measured by LV end-diastolic pressure, peak dp/dtmin, end-diastolic volume, and time constant of isovolumic pressure relaxation.

Analysis of Human MIs

Tissue sections derived from patients who died of ischemic MI presenting either as an acute, primary event (<5 days, n=4) or reoccurring infarction on the basis of old, healed MIs (n=4) were analyzed for biglycan by immunostaining (LF 51) and for collagen by Sirius red staining. The samples were collected for diagnostic purposes during autopsy and were examined by a senior pathologist (H.B.). Informed consent was obtained from patients or relatives. The present study was performed according to the Declaration of Helsinki, and the study protocol was approved by the Ethics Committee of the University Hospital of Essen.

Statistical Analysis

For multiple comparisons, 2-way ANOVA, followed by Bonferroni posttest, was performed. Values of P<0.05 were considered significant.

Results

Increased Biglycan Expression After MI

Real-time reverse-transcription polymerase chain reaction (RT-PCR) revealed strongly increased bgn mRNA expression in the LV after experimental MI, peaking 7 days after MI (Figure 1A). These results were confirmed by immunostaining for biglycan, showing that biglycan accumulation occurs in the infarcted ischemic area and border zone at 7 days (Figure 1C). Furthermore, at 7 days after MI, fibroblasts and inflammatory cells were detected in areas enriched with...
biglycan (online Data Supplement), in line with previous results in rats. At 14 days after MI, bgn mRNA levels were still 5-fold higher than in sham animals (Figure 1A), and biglycan immunostaining was still increased in the infarct and peri-infarct zones (Figure 1D).

**Cardiac Phenotype of Adult bgn<sup>−/−</sup> Mice**

bgn<sup>−/−</sup> mice were used as a model to study the effect of biglycan on cardiac function. First, the cardiac phenotype was analyzed in healthy, noninfarcted animals. At 6 months of age, morphological and hemodynamic analyses of the heart did not reveal any differences between WT and bgn<sup>−/−</sup> mice. In 15-month-old mice, the body weight (WT, 48.5 ± 4.5 g versus bgn<sup>−/−</sup>, 41.3 ± 5.2 g [mean ± SEM]; P < 0.05) and ratio of heart to body weight (Data Supplement) were slightly decreased. At 15 months, hemodynamic measurements in these mice revealed no differences in LV end-diastolic pressure, end-diastolic volume, end-systolic pressure, end-systolic volume (not shown), and heart rate (Data Supplement). However, ejection fraction showed a trend toward lower values, and end-diastolic pressure-volume ratios were decreased in bgn<sup>−/−</sup> mice (end-diastolic pressure-volume ratio: WT, 0.32 ± 0.11 mm Hg/μL; bgn<sup>−/−</sup>, 0.19 ± 0.07 mm Hg/μL [mean ± SEM]; n = 6; P < 0.05; Data Supplement). In addition, 15-month-old bgn<sup>−/−</sup> mice showed a trend toward decreased collagen type I mRNA expression but increased collagen type III and decorin expression as determined by real-time RT-PCR (data not shown). Morphological analysis and collagen staining showed no obvious difference between WT and bgn<sup>−/−</sup> mice at 15 months (Data Supplement), suggesting that both the morphology and cardiac ECM showed no major difference in noninfarcted bgn<sup>−/−</sup> mice.

**Decreased Survival After MI in bgn<sup>−/−</sup> Mice**

Kaplan-Meier analysis revealed higher mortality in bgn<sup>−/−</sup> mice after experimental MI. This increase in mortality was obvious after 7 days and continued until 3 weeks at the end of the study. At 3 weeks, the survival rates were 60% and 20% in WT and bgn<sup>−/−</sup> mice, respectively (Figure 2A). To investigate the cause of death, an additional group of animals (n = 8) underwent experimental MI and morphological analysis 7 days after MI. During this 7-day period, the animals were closely monitored, and mice that died underwent autopsy immediately. Analysis of this group revealed that the frequency of LV ruptures was ~33% in WT and 66% in bgn<sup>−/−</sup> mice, explaining the lower survival (Figure 2B). Figure 3 shows that the area at risk and infarct size were not different between the 2 genotypes as determined by Evans blue and p-nitro blue tetrazolium 7 days after MI. These data exclude the possibility that increased area at risk or infarct size is responsible for the higher frequency of rupture.

**Matrix Remodeling 7 Days After MI**

To investigate the mechanisms that caused LV ruptures, ECM remodeling was characterized in both groups. Collagen content of infarct scars was similar between genotypes as determined by Sirius red staining (bright field, Sirius red expressed as area fraction: WT, 21.9 ± 6.7% versus bgn<sup>−/−</sup>, 37.9 ± 7%; n = 4; P = 1.6). In addition, immunohistochemistry of collagen type I revealed no quantitative differences between groups (data not shown). In polarized light using the birefringence analysis, Sirius red staining revealed increased density of collagen in WT mice as indicated by the bright red (Figure 4C and 4D; Sirius red birefringence expressed as area fraction: bgn<sup>−/−</sup>, 3.9 ± 1% versus WT, 10.8 ± 1.7%; n = 4; P < 0.05). Furthermore, Movat’s pentachrome staining revealed a higher proportion of proteoglycans in scars of bgn<sup>−/−</sup> mice at 7 days after MI (Figure 4E and 4F), which was corroborated by Alcian blue staining and subsequent quanti-
The expression patterns of MMP-2, -8, -9, and -13 and TIMP-1, -2, and -4 were analyzed by immunostaining (Figure 4). Taken together, the infarct scars of bgn<sup>-/-</sup> mice were characterized by loosely packed collagen fibers and a higher amount of proteoglycans, including decorin.

The expression patterns of MMP-2, -8, -9, and -13 and TIMP-1, -2, and -4 were analyzed by immunostaining (Figure 5) and by real-time RT-PCR (Data Supplement). MMP-2, -8, -9, and -4 were strongly upregulated in the infarcted area compared with the noninfarcted area in both genotypes (Figure 5). The expression of MMP-2 and -13 was significantly higher in the infarcted area of bgn<sup>-/-</sup> mice compared with WT. However, MMP-9 was decreased and TIMP-1 and -4 were significantly upregulated in bgn<sup>-/-</sup> mice after experimental MI. The differences detected by immunostaining were largely paralleled by mRNA expression (Data Supplement). In situ zymography indicating gelatinolytic activity mainly through MMP-2 and -9<sup>-/-</sup> revealed no significant difference between genotypes (Figure 5P). Furthermore, the mRNA expression of procollagen-prolyl-4-hydroxylase, procollagen-lysyl-hydroxylase 2, procollagen-lysyl-hydroxylase 1, and tissue transglutaminase, key enzymes in the regulation of collagen and ECM crosslinking, was not differentially regulated between the genotypes after MI (Data Supplement).

**Hemodynamic Parameters**

No difference in cardiac hemodynamic parameters was detected between 16-week-old sham-operated WT and bgn<sup>-/-</sup> animals (Table), confirming the analysis of WT versus bgn<sup>-/-</sup> mice under normal conditions as mentioned above. In all animals, as predicted, MI caused a decrease in ejection fraction (%) and an increase in LV end-diastolic pressure (mm Hg), end-diastolic volume (μL), and end-systolic volume (μL) (Figure 6). Additional hemodynamic parameters are presented in the Table, indicating severe impairment of hemodynamic functions of WT and bgn<sup>-/-</sup> mice 3 weeks after MI such as a decrease in LV end-systolic pressure (mm Hg), dP/dtmax (mm Hg/s), and dP/dtmin (mm Hg/s) and increased τ (ms). The most important finding is that bgn<sup>-/-</sup> mice demonstrate significantly increased post-MI LV dilatation with increased LV end-diastolic volume and end-systolic volume and decreased ejection fraction compared with WT controls 21 days after MI (Figure 6A through 6D). Furthermore, bgn<sup>-/-</sup> mice demonstrated reduced stroke volume and cardiac output despite significantly increased heart rate (bpm) (Table), suggesting compensatory tachycardia. As an additional sign of cardiac dilatation and failure, LV end-diastolic pressure was significantly higher in the infarcted area of bgn<sup>-/-</sup> mice compared with WT-MI; #P<0.05 vs WT-MI; *P<0.001 vs WT-MI; **P<0.05 vs respective noninfarcted regions.
 Enhanced LV dilatation in E and F, MRI representative longitudinal sections showing additional hemodynamic parameters are given in the Table. Hemodynamic measurements in WT vs bgn−/− mice were characterized by decreased ejection fraction (EF; A) and LV end-diastolic pressure (Ped; B), LV end-diastolic volume (Ved; C), and LV end-systolic volume (Ves; D) (sham WT, n = 8; MI WT, n = 10; MI bgn−/−; n = 6). Additional hemodynamic parameters are given in the Table. Calculation of LV end-diastolic wall stress revealed increased wall stress in MI compared with WT in control conditions without MI, no difference was evident between LV rings from WT and bgn−/− mice that ruptured at 84 and 90 mN, respectively (Figure 7I). However, 21 days after MI, the force to rupture was dramatically decreased in bgn−/− mice compared with WT (146 mN).

**Matrix Remodeling 21 Days After MI**

Increased frequency of cardiac ruptures and decreased hemodynamic function of bgn−/− mice after MI and less tightly packed collagen at 7 days (Figure 4) point toward perturbed ECM remodeling in the infarct scar of bgn−/− mice. Therefore, ECM remodeling also was characterized at 21 days after MI. MI induced a marked upregulation of collagen type 1 and 3 mRNA as determined by real-time RT-PCR, which was significantly stronger in the bgn−/− mice (Figure 7A). Decorin mRNA showed a trend toward upregulation in WT versus bgn−/− mice 21 days after MI (Figure 7B). The overall collagen content was similar as evidenced by Sirius red staining (Figure 7C and 7D; total Sirius red expressed as area fraction: WT, 41 ± 3.9%; versus bgn−/−, 43.8 ± 11.7%; n = 4; P < 0.05) and collagen type 1 immunostaining (not shown). A striking difference appeared with respect to collagen organization (Figure 7C and 7D). Under polarized light, Sirius red staining revealed that the collagen present in the scar of bgn−/− mice was characterized by a lower percentage of tightly packed collagen (Figure 7E and 7F; Sirius red birefringence staining revealed that the collagen present in the scar of bgn−/− mice was characterized by a lower percentage of tightly packed collagen (Figure 7E and 7F; Sirius red birefringence expression as area fraction: WT, 11.1 ± 0.3% versus bgn−/−, 5.9 ± 1.4%; n = 4; P < 0.05). Immunohistochemistry showed still increased decorin accumulation (not shown); however, the difference was not as pronounced as detected at 7 days (Figure 4). Analysis of the collagen matrix by electron microscopy revealed tight and parallel packing of collagen fibrils in the scars of WT mice. In contrast, collagen fibril organization was perturbed in bgn−/− mice (Figure 7H). The tensile force to rupture LV rings ex vivo was determined to investigate whether the differences in matrix composition and organization correlate with changes of tensile strength. Under control conditions without MI, no difference was evident between LV rings from WT and bgn−/− mice that ruptured at 84 and 90 mN, respectively (Figure 7I). However, 21 days after MI, the force to rupture was dramatically decreased in LV rings derived from bgn−/− mice (69 mN) compared with WT mice (146 mN).

**Biglycan Accumulation in Human MI**

Tissue sections derived from patients who died of ischemic MI presenting as either an acute, primary event or reoccurring acute infarction on the basis of old healed MI were examined. Figure 8A through 8D represents an area from an acute MI characterized by acute myocyte necrosis with eosinophilic cytoplasm and without visible cardiomyocyte nuclei. Hardly any immunostaining for biglycan nor Sirius red staining of collagen was detected under these conditions. In contrast, Figure 8E through 8H depicts a healed infarction with fibrotic regions and some remaining vital cardiomyocytes. In these healed infarcts, strong accumulation of both biglycan and densely packed collagen as shown by birefringence analysis...
of Sirius red staining occurs (Figure 8F and 8H). Notably, biglycan colocalizes with tightly packed collagen. Thus, biglycan accumulates during healing and remodeling and associates with collagen after MI in human hearts.

**Discussion**

The key results of this study are increased mortality, high frequency of cardiac ruptures, and aggravated cardiac failure in \(bgn^{-/-}\) mice after experimental MI, which were likely the result of perturbed collagen remodeling in the infarct scar.

Seven days after experimental MI, thinning of the infarct area and formation of a collagen matrix occur in mice. After 14 days, a mature collagen-rich scar is established, and at this time point, collagen levels peak.\(^2,21\) Collagen type 1 is the major collagen of the myocardial ECM. Much attention has been focused on regulators of collagen expression and the breakdown of collagen matrixes during postinfarct remodeling. However, little is known about the role of small ECM molecules that govern collagen fibril formation. Among these small ECM molecules are the small leucine-rich proteoglycans such as biglycan and decorin. Small leucine-rich proteoglycans can be regarded as accessory ECM molecules at the interface of matrix assembly and signaling, which might have potential for therapeutic interventions. The aim of the present study was to investigate whether biglycan affects cardiac phenotype in healthy animals and, importantly, after experimental MI.

No differences were detected with respect to the cardiac phenotype at 6 months in WT versus \(bgn^{-/-}\) mice. At 15 months, the relaxation parameter \(\tau\) and the end-diastolic pressure-volume ratio were decreased in \(bgn^{-/-}\) mice. Although other parameters\(^22\)
may influence the end-diastolic pressure-volume ratio, this finding suggests that the intrinsic myocardial stiffness is reduced in aged \textit{bgn}^{-/-} mice. Taken together, these findings suggest that during physiological conditions \textit{bgn} deficiency has only minor effects on LV function, which starts to induce hemodynamic changes only during aging.

After experimental MI, biglycan expression was strongly upregulated in WT mice, as shown previously in rats. Interestingly, the upregulation was transient, peaking at 7 days, at the same time that collagen content also is highest. Using immunohistochemistry, we found biglycan in the infarct scar and border zone of the infarct at 7 and 14 days after MI, in line with a role of biglycan in collagen remodeling. During the whole experimental period, \textit{bgn}^{-/-} mice showed higher mortality after MI, which was due in large part to LV ruptures. In addition, spontaneous death without ruptures occurred more often in \textit{bgn}^{-/-} mice. This might be a consequence of aggravated cardiac failure and LV dilatation as indicated by increased LV end-diastolic volume, end-diastolic pressure, and ratios of wet lung weight to dry lung weight in \textit{bgn}^{-/-} mice after MI.

\textit{bgn}^{-/-} mice and WT mice showed no differences in the area at risk and infarct size, which excludes the possibility that decreased survival of \textit{bgn}^{-/-} mice after MI is a consequence of increased ischemia or necrosis. Birefringence analysis of Sirius red–stained sections revealed that the packing of collagen fibrils was disturbed in \textit{bgn}^{-/-} mice 7 and 21 days after MI. This was confirmed by analysis of the ultrastructure of collagen in the infarct scar, showing that the array of collagen was heavily perturbed in \textit{bgn}^{-/-} mice. The quantity of collagen accumulating in the scar was not decreased as analyzed by immunohistochemistry of collagen type 1 and Sirius red staining. In contrast, mRNA expression of collagen type 1 and collagen type 3 was increased even in \textit{bgn}^{-/-} mice, which might represent a compensatory mechanism.

Increased MMP activity is known to contribute to ventricular dilatation after MI, and expression of MMPs is highly increased in the infarcted area. The upregulation of MMP-2 and MMP-13 was opposed by upregulation of TIMP-1 and TIMP-4 and downregulation of MMP-9. MMP-9 is a key player in adverse ventricular remodeling after MI because MMP-9–dependent collagen degradation is associated with abnormal collagen fibril formation. However, ventricular ruptures did not occur in \textit{dcn}^{-/-} mice. Therefore, from the present study, it appears that the cardiac phenotype is even stronger in \textit{bgn}^{-/-} mice compared with \textit{dcn}^{-/-} mice. Furthermore, upregulation of decorin as observed in \textit{bgn}^{-/-} mice 7 days after MI was not sufficient to compensate for the loss of biglycan as it does with respect to the osteoporosis phenotype.

Analysis of scars of MI from humans revealed a strong accumulation of biglycan in close association with collagen in fibrotic areas of healed scars, whereas biglycan was not detected after acute human MI. It is therefore possible that the present findings are of clinical relevance and that biglycan might participate in the evolution of a collagenous ECM during healing of human MI. However, the present data do not allow a conclusion to be drawn as to whether biglycan deposition is characteristic for postinfarct remodeling or is associated with fibrotic remodeling and hypertrophy in general. LV wall rupture as observed in \textit{bgn}^{-/-} mice also is a complication of acute MI in patients that is responsible for \textit{20}\% of infarct-related deaths. Therefore, it might be of interest to investigate the patterns of biglycan expression in human MI and the relation to cardiac rupture in future studies. From the present study, it is obvious that the complete absence of biglycan is deleterious and prevents the establishment of a stable infarct scar and hemodynamic adaptation, suggesting that biglycan is required for proper infarct healing. However, future studies should address how much biglycan is needed for proper scar formation and whether too much biglycan might also have adverse effects such as enhanced fibrosis.

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Disclosures

None.

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Online Figure 1
Online Figure 2

A. Haert weight/body weight (x10^-3)

B. HR (min^-1)

C. Ecalc

D. Pressure-volume relationships

E. WT

F. bgn^-0
Online Figure 4

A

B

C

D

Online Figure 4

A

B

C

D