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Dysfunction of the ER chaperone BiP accelerates the renal tubular injury

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Abstract

Tubular-interstitial injury plays a key role in the progression of chronic kidney disease. Although endoplasmic reticulum (ER) stress plays significant roles in the development of chronic diseases such as neurodegenerative disease, cardiomyopathy and diabetes mellitus, its pathophysiological role in chronic renal tubular cell injury remains unknown. BiP is an essential chaperone molecule that helps with proper protein folding in the ER. Recently, we have produced a knock-in mouse that expresses a mutant-BiP in which the retrieval sequence to the ER is deleted in order to elucidate physiological processes that are sensitive to ER functions in adulthood. The heterozygous mutant-BiP mice showed significant tubular-interstitial lesions with aging. Furthermore, proteinuria induced by chronic protein overload accelerated the tubular-interstitial lesions in the mutant mice, accompanying caspase-12 activation and tubular cell apoptosis. These results suggest that the ER stress pathway is significantly involved in the pathophysiology of chronic renal tubular-interstitial injury in vivo.

Keywords: Endoplasmic reticulum stress; Chaperone; Tubular-interstitial injury; Protein overload nephropathy; Caspase-12

Chronic kidney disease (CKD), defined as kidney damage lasting more than 3 months [1], is a global public health problem. The significant correlation between the degree of tubular-interstitial injury and renal function indicates that tubular-interstitial injury plays a key role in CKD progression irrespective of the initial cause [2]. While proteinuria, ischemia, or some renal toxic drugs directly injure tubular cells, these factors are also known to induce endoplasmic reticulum (ER) stress in renal tubular cells [3–6].

Newly translated polypeptide chains are inserted into the ER and folded by interacting with molecular chaperones such as immunoglobulin binding protein (BiP). Aberrant protein folding due to extracellular stimuli such as ischemia, oxidative stress, or genetic mutation induces ER stress that initiates unfolded protein response (UPR), which alleviates protein overload in the ER [7]. If the stress continues or is beyond the capacity of the ER quality control, the overload of misfolded proteins seems to initiate an apoptotic process. The activation of IRE1 induces the expression of BiP as well as CHOP/GADD153 [8], a transcription factor that causes Bcl-2 down-regulation and cell death [9]. IRE1 also transduces signals to a cytosolic factor, TRAF2, that activates the JNK pathway [10] as well as the caspase-12 dependent apoptotic pathway [11]. These processes may play an important role in the development of chronic diseases such as neurodegenerative disease [12], cardiomyopathy [13], diabetes mellitus and arterial sclerosis [14]. In kidney diseases, tubular cell injuries by serum albumin [3], ischemia [4] and nephrotoxic chemicals such as paracetamol [5] and cysplatin [6] are reported to be associated with ER stress. However, all these studies adopted an acute tubular injury model. And so, the pathophysiological role of ER stress in chronic kidney injury still remains unclear.

BiP is an essential chaperone molecule that helps proper protein folding in the ER. The complete deletion of BiP

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causes cell death in yeast [15]. Recently, we have produced a knock-in mouse expressing a mutant-BiP in order to elucidate physiological processes that are sensitive to ER functions in adulthood [16]. The mutant-BiP lacks the retrieval carboxyl-terminal Lys-Asp-Glu-Leu (KDEL) sequence [17,18] that normally functions to return BiP to the ER from the secretory pathway by the KDEL receptor in the Golgi. This allowed us to examine the effects of a defect in ER functions without completely eliminating BiP functions. The homozygous mutant-BiP mice suffered from ER stress and survived only several hours after birth due to impaired pulmonary surfactant biosynthesis and respiratory failure [16]. The heterozygous mutant-BiP mice produced pulmonary surfactant and grew up to be apparently normal adults.

In order to elucidate the pathophysiological role of ER stress in chronic kidney injury, we analyzed the renal lesions of aged heterozygous mutant-BiP mice. The heterozygous mutant-BiP mice showed significant tubular-interstitial lesions with aging. Furthermore, proteinuria induced by chronic protein overload accelerated the tubular-interstitial lesions, accompanying caspase-12 activation and tubular cell apoptosis. These results suggest that the ER stress pathway is significantly involved in the pathophysiology of chronic renal tubular-interstitial injury.

Materials and methods

Reagent. Low-endotoxin BSA (A9430) was purchased from Sigma Chemical (St. Louis, MO). The following antibodies were used for Western blotting. Rabbit antiserum against caspase-12 (MBL, Nagoya, Japan), rabbit anti-serum against the HA epitope (Zymed), mouse monoclonal antibody (mAb) SPA-827 against BiP (KDEL sequence; Stressgen), rabbit antiserum against CHOP/GADD153, and mouse mAb against γ-tubulin (Sigma Chemical).

Mice. We used homologous recombination to establish knock-in mice expressing a mutant-BiP lacking the carboxyl-terminal KDEL sequence [16]. The missing KDEL sequence was replaced by a hemagglutinin (HA) tag. The heterozygous mutant-BiP mice have been maintained over ten generations with crossing to C57BL/6 mice. Mutant-BiP female mice, their wild type female littermates and C57BL/6 female mice (20–25 g, 25–40 weeks of age and more than 80 weeks of age) were used. All mice were provided with food and water *ad libitum* before the experiment. All animal experimental procedures were in accordance with a protocol approved by the Institutional Animal Care Committee of Chiba University, Chiba, Japan.

Induction of protein-overload nephropathy. Protein-overload nephropathy was induced as described previously [19]. Mice were nephrectomized with the left kidney under general anesthesia with pentbarbital (Dainippon Sumitomo Pharma, Osaka, Japan). Seven days later, endotoxin-free BSA (10 mg/body weight (g)) dissolved in saline was injected into the mice intraperitoneally five days per week for six consecutive weeks. Control mice received intraperitoneal injections of an equal volume of saline using an identical schedule. Twelve hours after the final BSA treatment, blood samples were taken, and the right kidney was removed under general anesthesia. The removed kidney was divided into two fragments which were frozen in liquid nitrogen or fixed in 4% paraformaldehyde, respectively.

Measurement of urinary protein excretion. The uninephrectomized mice treated with low endtoxin BSA (10 mg/body weight (g)) for 7 days were placed in metabolic cages individually 12 h after the final BSA injection and urine samples were obtained. Urinary protein was measured with the pyrogallol red method using a micro TP-AR kit (Wako Pure Chemical Industries, Ltd., Osaka, Japan). Urinary creatinine was measured with the enzymatic method using Pureauto S CRE-L kit (Daiichi pure Chemicals Co., Ltd., Tokyo, Japan).

Histochemistry. The kidneys were fixed in 4% paraformaldehyde for 24 h. After fixation, they were dehydrated in increasing concentrations of ethanol, embedded in paraffin wax. Sections of four μm thickness were stained with hematoxylin and eosin or with Masson-trichrome staining. The degree of tubular interstitial lesions in aged mice was classified as follows [20]. Grade 0: no lesions or minimal scattered tubular lesions. Grade 1: a few tubular basement membranes were thickened. Grade 2: multifocal areas of scattered dilated and atrophic tubules with thickened basement membrane. Grade 3: more pronounced tubular lesions with atrophy, cellular infiltration and mild interstitial fibrosis. Grade 4: marked tubular dilation with proteinaceous casts, more pronounced cellular infiltration, and interstitial fibrosis. Tubular-interstitial lesions in BSA-overload nephropathy were graded as follows [19]. Grade 0: no tubular (atrophy, casts and dilation) and interstitial (fibrosis and inflammation) change. Grade 1: change affecting <25% of the sample. Grade 2: change affecting 25% to 50% of the sample. Grade 3: change affecting 50 to 75% of the sample. Grade 4: change affecting 75 to 100% of the sample.

TUNEL staining. Paraffin sections with a thickness of four μm were stained with a commercial TUNEL staining kit (In situ Cell Death Detection Kit-AP; Roche Diagnostics, Mannheim, Germany). TUNEL positive tubular cells per section were counted.

Western blotting. Western blotting was performed as described previously [13]. Imaging was obtained by LAS1000 and Image Gauge software (Fuji Photo Film Co., Ltd., Tokyo, Japan).

Statistics. Statistical analyses were performed using one-way ANOVA and *t*-test by means of GraphPad Prism statistical software (GraphPad Software Inc. San Diego, CA).

Results

Homozygous mutant-BiP mice suffered from ER stress

The homozygous mutant-BiP knock-in mice died within 24 h after birth because of respiratory failure [16]. The neonatal mutant kidney apparently developed normally and showed no obvious histopathological abnormality at birth (Data not shown). However, we found that the expression of GRP94, an ER chaperone, as well as CHOP/GADD153, a cell death-related transcriptional factor during the UPR, was enhanced in the homozygous mutant-BiP kidney by Western blotting (Fig. 1), suggesting that the mutant kidney suffered from ER stress.

Heterozygous mutant-BiP knock-in mice developed marked tubular-interstitial lesions with aging

The heterozygous mutant-BiP mice grew up to be adults and showed apparently normal kidney development. However, some aged mice developed a severe tubular-interstitial lesion which consisted of tubular atrophy, tubular luminal dilatation and interstitial fibrosis (Fig. 2A). The tubular-interstitial damage was scored as described in Materials and methods. The tubular damage score of aged mutant-BiP mice was significantly higher than that of the wild type (Fig. 2B). Thus, mutant-BiP mice over 80 weeks of age showed more severe tubular-interstitial lesions than age-matched wild type mice.

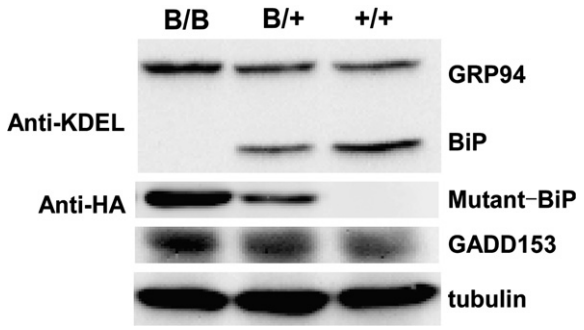

Fig. 1. Neonatal kidney of homozygous mutant-BiP knock-in mice suffered from ER stress. Western blotting of GRP94, BiP, CHOP/GADD153 and γ-tubulin in neonatal kidneys of homozygous (B/B), heterozygous (B/+) mutant-BiP knock-in mice and wild type (+/+) mice (P1). Anti-KDEL antibody recognized wild type BiP and GRP94. Anti-HA antibody recognized only mutant-BiP.

BSA-overload proteinuria exacerbated renal injury in heterozygous mutant-BiP mice

Proteinuria plays a key role in the tubular cell injury involved in human kidney disease [21]. We used the bovine serum albumin (BSA)-overload proteinuria mouse model to clarify whether the tubular cell injury induced by proteinuria is associated with the tubular-interstitial lesions observed in aged heterozygous mutant-BiP mice. BSA was injected into young mutant-BiP mice (25–40 weeks of age) and control wild type mice intraperitoneally 5 days per week for 6 weeks after the uninephrectomy. While the mutant-BiP mice maintained renal tissue apparently as normal as the wild type mice, the BSA treatment caused severe tubular-interstitial injury only in the mutant-BiP mice (Fig. 3A and B). The mutant-BiP mice with BSA overload had a significantly higher tubular damage score than the wild type mice. Furthermore, the serum creatinine level of the BSA-treated mutant-BiP mice was also significantly higher than that of the wild type mice, indicating that proteinuria impaired the renal function of the mutant mice (Fig. 3C). No significant difference in creatinine level was observed between the control wild type mice and the mutant-BiP mice without BSA treatment (data not shown).

In order to determine whether the differences in renal injury with BSA treatment between heterozygous mutant-BiP mice and wild type mice could be due to different levels in urinary protein excretion, we examined the urinary protein of the two different groups. After the uninephrectomy, BSA (10 mg/body weight(g)) was injected intraperitoneally into the mice once a day for 7 days and urinary protein excretion was examined on day 8. As shown in Fig. 3D, we did not find any significant differences in urinary protein excretions between the mutant-BiP mice and wild type mice. Thus, these results suggest that the tubular-interstitial tissue of the mutant-BiP mice is more sensitive to proteinuria than that of the wild type mice.

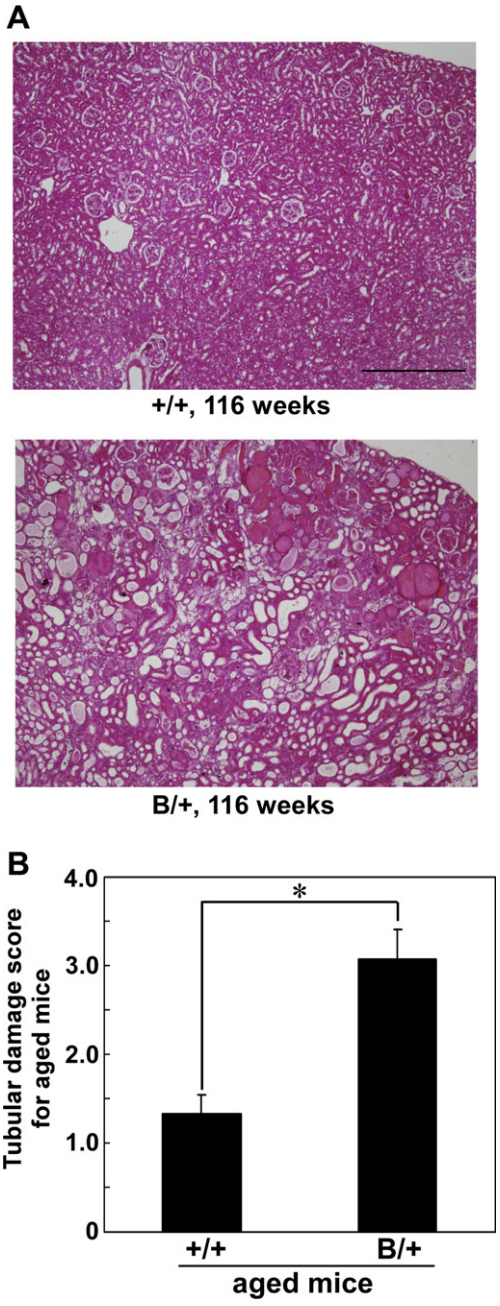

Fig. 2. Heterozygous mutant-BiP knock-in mice developed marked tubular-interstitial lesions with aging. (A) Representative sections of the renal cortex of aged wild type (+/+) and heterozygous mutant-BiP mice (B/+) (116 weeks of age, respectively) with hematoxylin and eosin staining. Magnification 40×. A scale bar indicates 500 μm. (B) The tubular damage score of aged mutant-BiP mice (B/+) over 80 weeks of age was significantly higher than that of the wild type (+/+). The bargraph represents mean ± SEM. $N = 6$ (+/+) and 6 (B/+). $^{*}P < 0.01$.

Caspase-12 activation and tubular cell apoptosis occurred in the kidneys of BSA-treated heterozygous mutant-BiP knock-in mice

BSA is reported to cause apoptosis in a murine proximal tubular cell line through a caspase-12 dependent apoptotic-pathway induced by ER stress [3]. In order to detect apoptosis in the BSA-treated tubular-interstitial lesions of het-

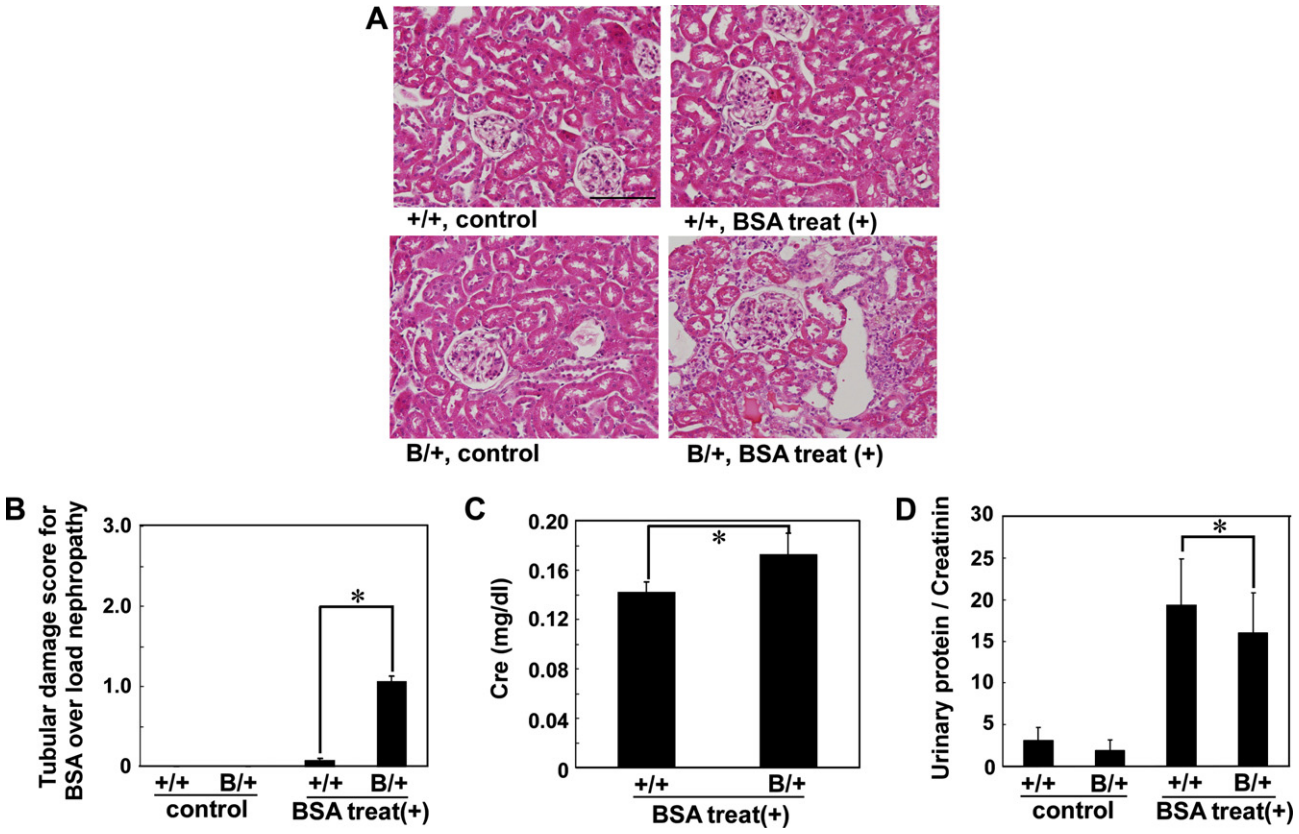

Fig. 3. BSA-overload proteinuria exacerbated the renal injury in heterozygous mutant-BiP mice. (A) Representative sections of the renal cortex of wild type (+/+) and heterozygous mutant-BiP mice (B/+) without or with BSA-overload treatment (40 weeks of age respectively) with hematoxylin and eosin staining. Magnification 200×. A scale bar indicates 100 μm. (B) Tubular damage score of wild type (+/+) and heterozygous mutant-BiP mice (B/+) without or with BSA overload treatment. The mutant-BiP mice with BSA overload obtained a significantly higher tubular damage score than did the wild type mice. The bargraph represents mean ± SEM. $N = 5$ (+/+, control), 4 (B/+, control), 5 (+/+, BSA treat+) and 6 (B/+, BSA treat+). $^{*}P < 0.01$ (C) The serum creatinine level of the BSA-treated mutant BiP mice (B/+) was significantly higher than that of the wild type mice (+/+). The bargraph represents mean ± SEM. $N = 5$ (+/+, BSA treat+) and 6 (B/+, BSA treat+). $^{*}P < 0.05$. (D) Urinary protein excretions in the BSA-overload proteinuria model did not differ between heterozygous mutant-BiP knock-in mice and wild type mice. The excretion level of urinary protein was evaluated by urinary protein concentration (mg/dl) / urinary creatinine concentration (mg/dl) in wild type (+/+) and heterozygous mutant-BiP knock-in mice (B/+) without or with BSA-overload treatment. The bargraph represents mean ± SEM. $N = 3$ (+/+, control), 3 (B/+, control), 6 (+/+, BSA treat+) and 6 (B/+, BSA treat+). $^{*}P > 0.05$ (not significant).

erozygous mutant-BiP mice, we performed TUNEL staining. The number of TUNEL positive tubular cells in BSA-treated mutant-BiP mice was significantly higher than that in the wild type (Fig. 4A and B). We also found the activation of caspase-12 in the BSA-treated mutant mice kidney by Western blotting that showed the cleavage of caspase-12 (Fig. 4C and D). Taken together, these results suggest that the renal tissue of the mutant-BiP mice suffers from ER stress and is sensitive to proteinuria, which may cause tubular-interstitial lesions and apoptosis through ER stress pathway.

Discussion

In this study, we showed, for the first time, that the mutation of an ER chaperone molecule caused renal tubular-interstitial lesions in vivo with aging, and that chronic BSA-overload proteinuria exacerbated the lesions. Importantly, our results suggest not only that ER stress participates in the common mechanisms of chronic kidney disease progression but also that ER related molecules and their genes are likely candidates for deterioration as chronic kidney disease progresses.

Age related tubular-interstitial injury has been mainly investigated in rat models, and the involvement of myofibroblast activation and extracellular matrix accumulation [20], ischemia [22] and proteinuria [23] has been suggested. Among these, we focused on the pathophysiological role of proteinuria because it is strongly associated with the progression of chronic kidney disease in human [21]. We used the BSA-overload proteinuria model to accelerate chronic tubular-interstitial injury in heterozygous mutant-BiP mice. This experimental model is widely used to cause tubular-interstitial injury since it is able to induce protein overload in renal tubular cells in primarily non-hemodynamic and non-immunologic settings. In mice, the renal response to albumin overload has been reported to be strain-dependent and was not impressive in the C57BL/6

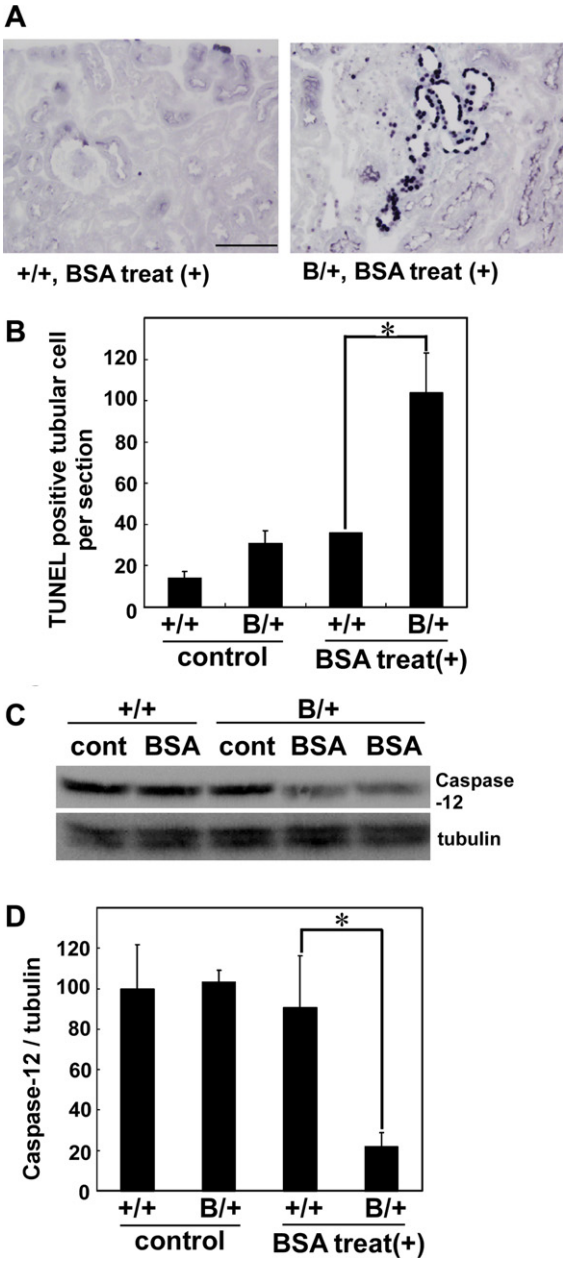

Fig. 4. Caspase-12 activation and tubular cell apoptosis occurred in the kidneys of BSA-treated heterozygous mutant-BiP knock-in mice. (A) Representative sections of the renal cortex of BSA treated wild type (+/+) and heterozygous mutant-BiP mice (B/+) with TUNEL staining. Magnification 200×. A scale bar indicates 100 μm. (B) The number of TUNEL staining positive tubular cells in the renal cortex per section of wild type (+/+) and heterozygous mutant-BiP mice (B/+) without or with BSA overload treatment. The bargraph represents mean ± SEM. $N = 4$ (+/+, control), 4 (B/+, control), 4 (+/+, BSA treat+) and 4 (B/+, BSA treat+). $^{*}P < 0.05$. (C) Western blotting of pro-caspase-12 in the kidneys of wild type (+/+) and heterozygous mutant-BiP mice (B/+) without or with BSA-overload treatment. (D) Densitometoric analysis of the relative expression level of pro-caspase-12 compared to that of tubulin. The expression of pro-caspase-12 in BSA-treated mutant-BiP kidneys was significantly less than in wild type kidneys. The bargraph represents mean ± SEM. $N = 4$ (+/+, control), 4 (B/+, control), 4 (+/+, BSA treat+) and 4 (B/+, BSA treat+). $^{*}P < 0.05$.

strain that was used in the present study [24]. Indeed, we did not observe pathological renal changes in the wild type C57BL/6 mice following the BSA-overload proteinuria. However, the heterozygous mutant-BiP mice suffered severe tubular-interstitial lesions and tubular cell apoptosis due to protein-overload proteinuria. Since the proteinuric levels were not different between the mutant-BiP mice and the wild type mice, the severe tubular-interstitial injury in the mutant mice was conjectured to be caused by their high susceptibility to albumin induced tubular cell injury. Indeed, we found that aged mutant-BiP mice developed severe tubular-interstitial lesions which consisted of tubular atrophy, tubular luminal dilatation and interstitial fibrosis, even without protein overload.

The involvement of ER stress and its downstream caspase-12 dependent apoptotic pathway on tubular cell injury induced by proteinuria have been reported [3]. Aged heterozygous mutant-BiP mice showed glomerular lesion consisting of mesangial matrix increase and glomerular sclerosis. While we could not exclude the contribution of the glomerular lesion, high susceptibility to proteinuria due to potential ER dysfunction may cause the tubular-interstitial lesion of aged heterozygous mutant-BiP mice.

BiP is a major molecular chaperone in the ER and participates in protein folding and ER stress related signal transduction [25]. In murine embryonic fibroblast of homozygous mutant-BiP mice, mutant BiP escapes from the ER, and ER stress is induced to compensate for it [16]. We found that ER stress is induced in the homozygous mutant-BiP kidney. Heterozygous mutant-BiP mice express both the wild type BiP and the mutant BiP, and ER stress is not induced in the steady state. However, it is possible that potential vulnerability to ER stress may exist in the tubular cells of heterozygous mutant-BiP mice and result in severe tubular injury during periods of chronic stress such as aging and proteinuria. Tubular cells are most sensitive to ER stress when mice are injected with tunicamycin that disturbs protein glycosylation in the ER and causes ER stress, which results in acute renal tubular necrosis [26]. Consistently, we found caspase-12 activation in the kidneys of BSA-treated mutant-BiP mice, indicating that the ER stress pathway may have been involved in the BSA-mediated tubular-interstitial injury.

Our results also suggest that ER stress would be a promising therapeutic target with which to combat kidney diseases. In order to treat ER stress related diseases, two kinds of strategy will be effective: the promotion of protein folding in the ER and the inhibition of an ER stress induced apoptotic pathway. Indeed, the administration of chemical chaperones that promote protein folding in the ER has been reported to be effective in treating type2 diabetes, which has been speculated to be caused by ER stress after experiments using a mouse model [27]. The heterozygous mutant-BiP knock-in mice used in our experiments will be a suitable tool for investigating the relationship between ER stress and renal tubular-interstitial injury. Further investigations will be needed to clarify the role of ER stress in kidney diseases and to establish an ER stress targeted therapy.

Acknowledgments

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