PERK/IRE1α通路介导的肾细胞凋亡：GRP78/CHOP在狼疮性肾炎中的诊断价值

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摘要：目的 明确狼疮性肾炎（LN）患者血清中内质网应激（ERS）蛋白GRP78/CHOP含量变化，分析其诊断价值及蛋白表达改变对应的肾脏病理特征。**方法** 基于系统性红斑狼疮（SLE）多中心队列研究建立样本库，随机抽取LN患者60例和无肾脏受累的SLE患者35例，ELISA法检测GRP78和CHOP在患者血清中的含量，分析其与临床特征的相关性以及对LN和LN活动期的诊断能力。以MRL/lpr小鼠为LN动物模型，检测小鼠血清GRP78和CHOP表达及肾脏中内质网凋亡相关指标。**结果** LN患者血清GRP78和CHOP高于无肾脏受累的SLE患者（$P<0.05$）；GRP78和CHOP在LN活动期患者中也高于稳定期患者（$P<0.05$）；关联分析提示血清GRP78和CHOP水平与SLEDAI评分、24 h尿蛋白正相关；ROC结果显示CHOP对LN（AUC=0.762）和LN活动（AUC=0.933）具有较高的诊断能力。与临床结果类似，LN小鼠GRP78和CHOP升高（$P<0.05$），而与该指标相关的PERK和IRE1α通路蛋白在肾脏中表达也升高（$P<0.05$），TUNEL染色显示LN小鼠肾脏细胞凋亡增加，凋亡相关蛋白表达升高（$P<0.05$）。**结论** GRP78/CHOP在狼疮性肾炎中的表达升高，可能与PERK/IRE1α双通路介导的ERS凋亡相关。
关键词：狼疮性肾炎；内质网应激通路；凋亡；GRP78；CHOP；PERK/IRE1α

Elevated expressions of GRP78/CHOP in lupus nephritis: their diagnostic value and association with PERK/IRE1α pathway-mediated renal cell apoptosis

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Abstract: Objective To examine the changes in serum levels of endoplasmic reticulum stress (ERS) proteins GRP78/CHOP in patients with lupus nephritis (LN) and analyze their diagnostic value and association with renal pathological features. **Methods** From a sample bank established based on a multicenter cohort study of systemic lupus erythematosus (SLE), 60 LN patients and 35 SLE patients without renal involvement were randomly selected. ELISA was used to detect serum levels of GRP78 and CHOP in the patients to analyze their correlation with clinical features and their diagnostic ability for LN and active LN. MRL/lpr mice were used as an animal model of LN to examine their serum levels of GRP78 and CHOP expression and renal expressions of endoplasmic reticulum apoptosis-related proteins. **Results** Serum GRP78 and CHOP levels were significantly higher in LN patients than in SLE patients without renal involvement ($P<0.05$), and were also higher in active LN patients than in patients in the stable phase ($P<0.05$). Correlation analysis indicated that serum GRP78 and CHOP levels were positively correlated with SLEDAI scores and 24-h urinary protein. ROC analysis showed that CHOP had a high diagnostic ability for LN (AUC=0.762) and active LN (AUC=0.933). Consistent with the clinical findings, serum GRP78 and CHOP levels were elevated in LN mice, and the expressions of PERK and IRE1α pathway proteins were also increased in the kidneys of the mice. TUNEL staining showed increased renal cell apoptosis and elevated renal expressions of apoptosis-related proteins in LN mice. **Conclusion** Serum levels of GRP78/CHOP are increased in LN patients possibly in association with ERS-induced apoptosis mediated by the PERK/IRE1α dual pathway.
Keywords: lupus nephritis; endoplasmic reticulum stress pathway; apoptosis; GRP78; CHOP; PERK/IRE1α

狼疮性肾炎（LN）是系统性红斑狼疮（SLE）中最常见和最严重的器官受累之一[1]。疾病活动时，肾驻留细胞出现不可逆损伤是LN进展的重要原因[2, 3]。蛋白质分泌增加或折叠中断会导致错误蛋白质在内质网积聚，被称为内质网应激（ERS）[4, 5]。过度的ERS过程会诱导细胞细胞异常凋亡[6]，是肾驻留细胞损伤的重要原因[7]。但LN是否与ERS诱导肾驻留细胞损伤有关，ERS蛋白是否能提示疾病活动，仍需研究阐明。

相对分子质量78 000葡萄糖调节蛋白（GRP78）是内质网伴侣蛋白[8]和ERS起始控制蛋白[9]。C/EBP同源蛋白（CHOP）是ERS诱导凋亡的标志信号[10]。GRP78和CHOP与急性肾损伤和肾纤维化等病理变化相关[11-13]，但是否参与LN发病还不明确[14]。本研究初步探明了GRP78和CHOP在LN患者血清中含量变化及其可能的诊断价值，并通过动物实验探索ERS介导LN肾驻留细胞凋亡的分子通路，为LN肾损伤的发病机制提供新的理论支持。

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1 材料和方法

1.1 研究资料

从系统性红斑狼疮多中心队列研究建立的样本库中随机选取符合2009年ACR的SLE诊断标准，同时存在肾脏损害、已诊断为LN的患者60例。按肾脏损害的临床表现（持续性尿蛋白>0.5 g/d，出现红细胞、血红蛋白、颗粒惯性或混合型细胞管型尿，多次尿蛋白>+++）评价LN活动，将LN患者分为活动期（30例）和稳定期（30例）2个亚组。纳入标准：入院前未使用保肾药及利尿剂等药物；既往无精神障碍史；可自由交流和沟通；未使用激素、免疫抑制剂、生物制剂等药物。排除标准：孕妇；近3个月有手术、创伤史；心肝功能严重异常者；排除感染、恶性肿瘤、心功能不全、泌尿系结石等对肾损害的疾病。同期选择符合2009年ACR的SLE诊断标准，与LN患者疾病活动度相近，但无肾脏受累的SLE患者35例作为对照。比较两组对象的一般资料、临床指标（SLE疮疾病活动性指数（SLEDAI）、抗dsDNA抗体、抗Sm抗体、24 h尿蛋白定量、补体C3和C4、红细胞、白细胞、血小板、血红蛋白）的差异。LN组及SLE组均纳入临床信息完整的患者，均签署知情同意书，本研究经浙江中医药大学附属第二医院伦理委员会审批同意（伦理批号：2020-KL-002-IH01）。

1.2 实验动物

7周龄MRL/lpr小鼠8只作为LN模型组，C57BL/6小鼠8只作为健康对照组，均购于上海斯莱克实验动物有限公司，饲养于SPF环境中，本实验严格遵守浙江中医药大学实验动物管理伦理委员会的相关规定（伦理批号：IACUC-20211108-12）。小鼠自由采食专用灭菌饲料，自由饮水，适应性喂养1周后开始试验，两组小鼠隔周用代谢笼留取尿液检测24 h尿蛋白含量，8周后取血、处死并分离肾脏用于后续检测。

1.3 试剂和仪器

ELISA试剂盒：人GRP78、人CHOP（杭州圣隆生物科技有限公司）；小鼠CHOP（武汉菲恩生物科技有限公司）；小鼠白细胞介素6（IL-6）、肿瘤坏死因子α（TNF-α）（湖南艾方生物科技有限公司）；小鼠GRP78、抗dsDNA抗体（武汉华美生物有限公司）；Bradford蛋白定量试剂盒（上海碧云天生物技术有限公司）；肌酐检测试剂盒（南京生物工程研究所）；抗体Caspase3、cle-Caspase3、Bax、Bcl-2、JNK、pJNK（Cell Signaling Technology）；抗体PERK、pPERK、ATF4、IREα、pIREα、CHOP抗体（Affinity）；酶标仪（Thermo Fisher Scientific）；电泳仪和Western blotting成像分析仪（Biorad）；荧光显微镜（Olympus）。

1.4 实验方法

1.4.1 ELISA血清学检测 清晨采集研究对象静脉血4 mL，静置分层后离心，取上层血清待用；小鼠取血，静置分层后离心，分离上层血清待用；将小鼠血清按各ELISA试剂盒说明书要求稀释，并进行操作，检测人血清中GRP78、CHOP水平，小鼠血清中抗dsDNA抗体、IL-6、TNF-α、GRP78、CHOP水平。

1.4.2 病理染色 小鼠处死后取一侧肾脏固定于4%多聚甲醛中，脱水包埋后切片。将切片脱蜡、水化后，按染色试剂盒要求操作，对小鼠肾脏切片分别进行HE、PAS染色，中性树脂封固后，在显微镜下观察各组肾脏病理变化。

1.4.3 免疫荧光检测肾脏IgG沉积 将肾脏石蜡切片进行脱蜡、水化，抗原修复，山羊血清封闭，用山羊抗小鼠IgG抗体直接染色，用含DAPI的封片剂进行封片后，在荧光显微镜下观察荧光面积。

1.4.4 TUNEL染色 对小鼠肾脏切片进行TUNEL染色。将肾脏切片进行脱蜡、水化，使用Proteinase K通透10 min，PBS清洗3次，按说明书要求配置TUNEL标记液，37 ℃下孵育1 h，PBS终止标记，稍晾干后用含DAPI的封片剂进行封片。在荧光显微镜下观察细胞凋亡情况。

1.4.5 Western blotting 使用RIPA缓冲液提取小鼠肾脏组织中的总蛋白。用凝胶电泳法分离目标蛋白，并转移到聚偏氟乙烯膜上，封闭后用稀释的一抗4 ℃孵育过夜（一抗稀释比例均为1∶1000），洗膜后，二抗常温孵育2 h，将膜暴露在化学发光底物中进行显影。

1.5 统计学分析

数据用SPSS 22.0统计软件进行分析；正态分布计量资料以均数±标准差描述，采用T检验或秩和检验对两组计量资料进行比较，定性资料采用Fisher确切概率法进行比较。采用Pearson相关分析及多元线性逐步回归分析明确变量之间的相关关系；采用Spearman秩相关分析非正态分布的资料，且均为双侧检验，当$P<0.05$时认为差异有统计学意义。

2 结果

2.1 一般资料比较

两组间年龄、性别、BMI、SLEDAI、病程、抗dsDNA抗体、抗Sm抗体、血红蛋白、血小板、白细胞、补体C3、补体C4差异无统计学意义，LN组24 h尿蛋白含量明显高于SLE组（$P<0.05$，表1）。

2.2 LN患者血清GRP78和CHOP变化

与无肾脏受累的SLE组相比，LN组患者血清中GRP78和CHOP的水平明显升高（$P<0.05$，图1A、B）；对LN活动和稳定期两个亚组进行分析时，活动期LN患者血清中GRP78和CHOP的水平明显高于静止期患者（$P<0.05$，图1C、D）。

表1 LN组和SLE组间一般资料比较

Tab.1 Comparison of general clinical data between the patients in LN group and SLE group

Item	LN (*n*=60)	SLE (*n*=35)	*P*
Age (year, *Mean*±*SD*)	41.31±2.08	38.24±2.73	0.28
Female [*n* (%)]	56 (93.33%)	33 (94.29%)	0.85
BMI (kg/m^2)	21.84±0.60	22.99±0.98	0.35
SLEDAI	8.14±0.74	5.25±0.58	0.05
Illness duration (year)	8.18±1.33	8.90±1.90	0.57
24 h UTP (g/d)	1192.82±243.66	119.17±24.58	0.00
Anti-dsDNA[+(%)]	24 (40%)	11 (31.43%)	0.40
Anti-Sm[+(%)]	13 (21.67%)	8 (22.86%)	0.89
Hb (g/L)	115.25±3.04	123.04±5.66	0.10
PLT (10^9/L)	188.19±10.36	213.90±13.08	0.31
WBC (10^{12}/L)	5.81±0.50	5.68±0.49	0.63
C3 (g/L)	0.70±0.04	0.74±0.04	0.80
C4 (g/L)	0.14±0.02	0.12±0.02	0.20

BMI: Body mass index; SLEDAI: Systemic lupus erythematosus disease activity index; 24 h UTP: 24h-urinary total protein; Anti-dsDNA: Anti-double Stranded DNA Antibody; Anti-Sm: Anti-Smith Antibody; Hb: Hemoglobin; PLT: Platelet count; WBC: White blood cell count; C3: Complement component 3; C4: Complement component 4.

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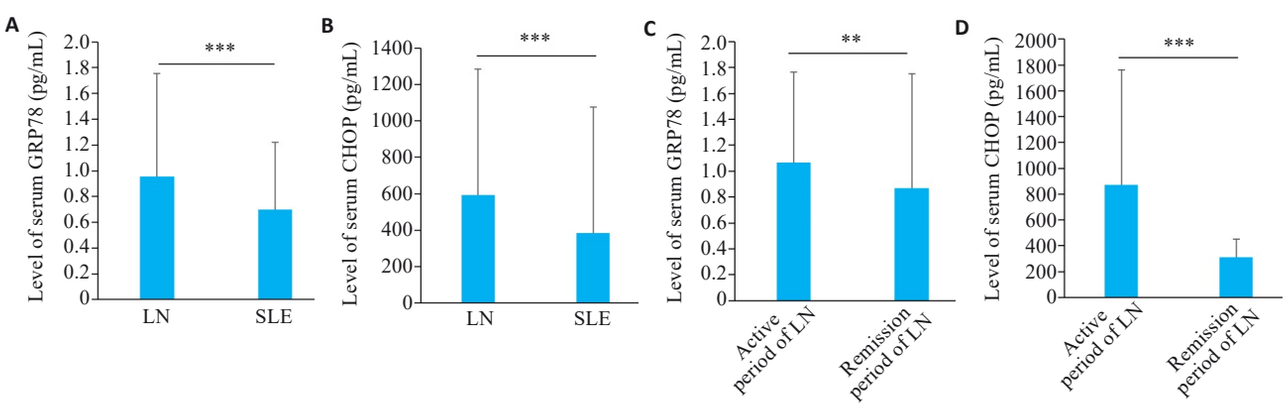

图1 LN和SLE患者血清中GRP78和CHOP水平

Fig.1 Level of serum GRP78 and CHOP in LN and SLE patients. **A**: Serum level of GRP78 in LN and SLE patients. **B**: Serum level of CHOP in LN and SLE patients. **C**: Serum level of GRP78 in LN patients in active and remission phase. **D**: Serum level of CHOP in LN patients in active and remission phase. ***P*<0.01, ****P*<0.001.

2.3 GRP78和CHOP与临床指标的相关性

LN患者中，血清GRP78和CHOP含量与SLEDAI评分、24 h尿蛋白含量具有正相关性（*P*<0.05），与白细胞数量、血小板数量、血红蛋白含量、补体C3、C4水平的相关性无统计学意义（*P*>0.05，图2）。

2.4 GRP78和CHOP对LN和LN活动的诊断能力

CHOP对LN（AUC=0.762，Cut-off value=324.7，Sensitivity=0.833，Specificity=0.743）和LN活动

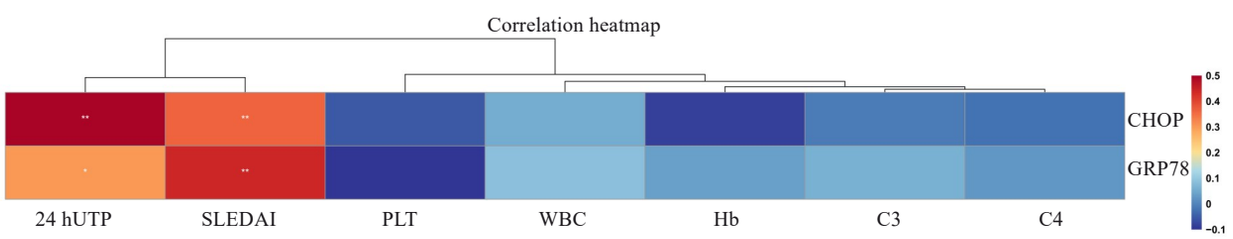

图2 GRP78和CHOP与临床指标相关性

Fig.2 Correlation of GRP78 and CHOP with clinical parameters in LN patients. **P*<0.05, ***P*<0.01.

（AUC=0.933，Cut-off value=380.4，Sensitivity=0.967，Specificity=0.8）具有较高的诊断价值。GRP78对LN（AUC=0.708，Cut-off value=659.5，Sensitivity=0.767，Specificity=0.657）和LN活动（AUC=0.696，Cut-off value=711.0，Sensitivity=0.767，Specificity=0.667）具有一定诊断价值（图3）。

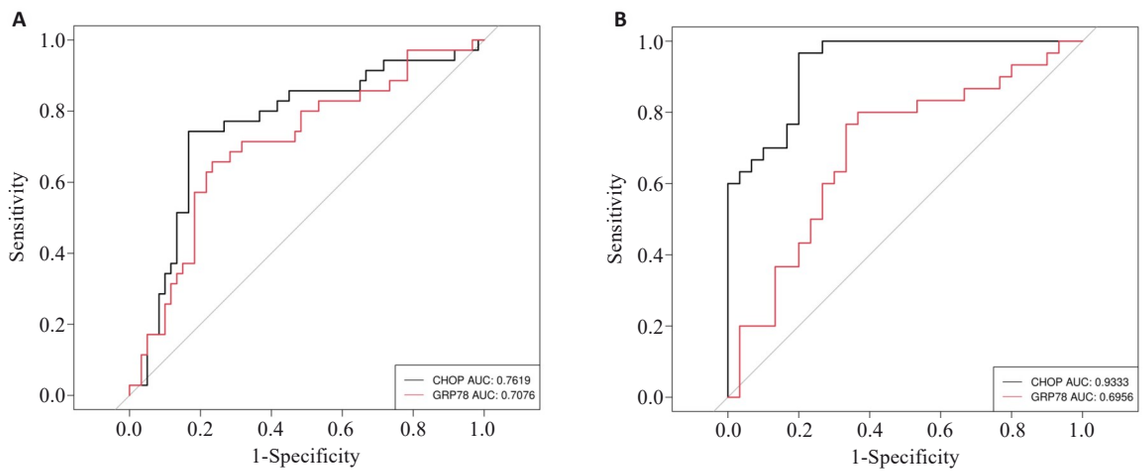

图3 GRP78和CHOP对LN的诊断能力

Fig.3 Diagnostic capabilities of GRP78 and CHOP for LN. **A**: ROC curves of peripheral blood GRP78 and CHOP for diagnosing LN. **B**: ROC curves of GRP78 and CHOP for diagnosis of LN in the active phase.

2.5 LN小鼠全身和肾脏表现

LN小鼠血清中IL-6、TNF-α和抗dsDNA抗体均明显高于Control组小鼠（$P<0.05$，图4A~C）。病理结果显示LN小鼠肾脏出现明显的系膜增生（图4D蓝箭头）、肾间质大量淋巴细胞浸润（图4D绿箭头）、基底膜增厚（图4D红箭头）。免疫荧光显示LN组肾脏存在“满堂亮”样IgG沉积（图4D）。

2.6 小鼠血清GRP78和CHOP水平

与临床的结果相似，在动物实验中，LN小鼠血清中GRP78和CHOP的水平均明显高于Control组小鼠（$P<0.05$，图5）。

2.7 LN小鼠肾脏细胞凋亡增加

与Control组相比，LN组肾小球和肾小管中均出现明显的荧光（图6A）；而凋亡相关蛋白Bax和cle-Caspase3在LN组肾脏中表达明显升高，Bcl2蛋白的表达降低（图6B、C）。

2.8 LN小鼠肾脏ERS凋亡相关蛋白表达增加

LN组PERK、IREα、JNK蛋白的磷酸化水平升高（$P<0.05$），PERK、IREα、JNK本体蛋白表达量在组间无明显差异；ATF4、CHOP蛋白表达量升高（$P<0.05$，图7）。

3 讨论

LN是一种肾小球肾炎，是SLE最严重的器官表现之一[15]。LN反复活动会造成肾脏不可逆损伤，早诊早治有助于延缓LN进展，改善患者预后[3, 16]。本研究对LN患者血清中GRP78和CHOP蛋白的含量进行检测，发现在LN患者血清中两种蛋白的表达均高于无肾脏受累的SLE患者，在活动期患者血清中含量也高于稳定期患者。ROC曲线显示CHOP对LN具有更明显的诊断价值，相关性分析则提示CHOP和GRP78水平与疾病活动度和24 h尿蛋白明显正相关。动物实验使用的MRL/lpr小鼠作为LN动物模型，存在与LN患者相似的全身炎症、高水平的自身抗体，肾内也存在与患者类似的肾小球系膜增生、炎性浸润、免疫复合物沉积的表现。由于GRP78是ERS起始的标志蛋白，而CHOP与ERS诱导的细胞凋亡密切相关，本研究在动物实验中检测了LN小鼠凋亡指标和ERS通路相关蛋白的表达变化。TUNEL染色显示LN小鼠肾脏凋亡细胞增多，且凋亡蛋白Bax和cle-Caspase3表达升高、Bcl2表达降低也提示着肾脏内细胞凋亡增加。ELISA结果显示LN小鼠血清中GRP78和CHOP含量升高，这一现象与临床结果一致；肾脏内ERS经典通路PERK和IRE1α及下游调控凋亡的蛋白表达增加，提示LN肾脏中存在ERS诱导的细胞凋亡。

当受到内源或外源性因素的刺激时，内质网中的未折叠或错误折叠蛋白会迅速积累，产生ERS[17]。ERS通过未折叠蛋白反应信号恢复正常折叠过程，但当ERS持续时间过长不可恢复时，该信号通路则会诱导细胞凋亡[18, 19]。GRP78作为ERS的主要传感器，与从内质网脱离激活PERK、IRE1α形成磷酸化二聚体，活化的PERK、IRE1α除进一步促进GRP78表达外，通过PERK/ATF4/CHOP通路和IRE1α/JNK/CHOP通路诱导细胞凋亡过程[20-25]。本研究发现LN小鼠肾脏中PERK和IREα的磷酸化升高；下游蛋白ATF4、CHOP表达增加，JNK蛋白磷酸化水平升高，小鼠血清中游离的

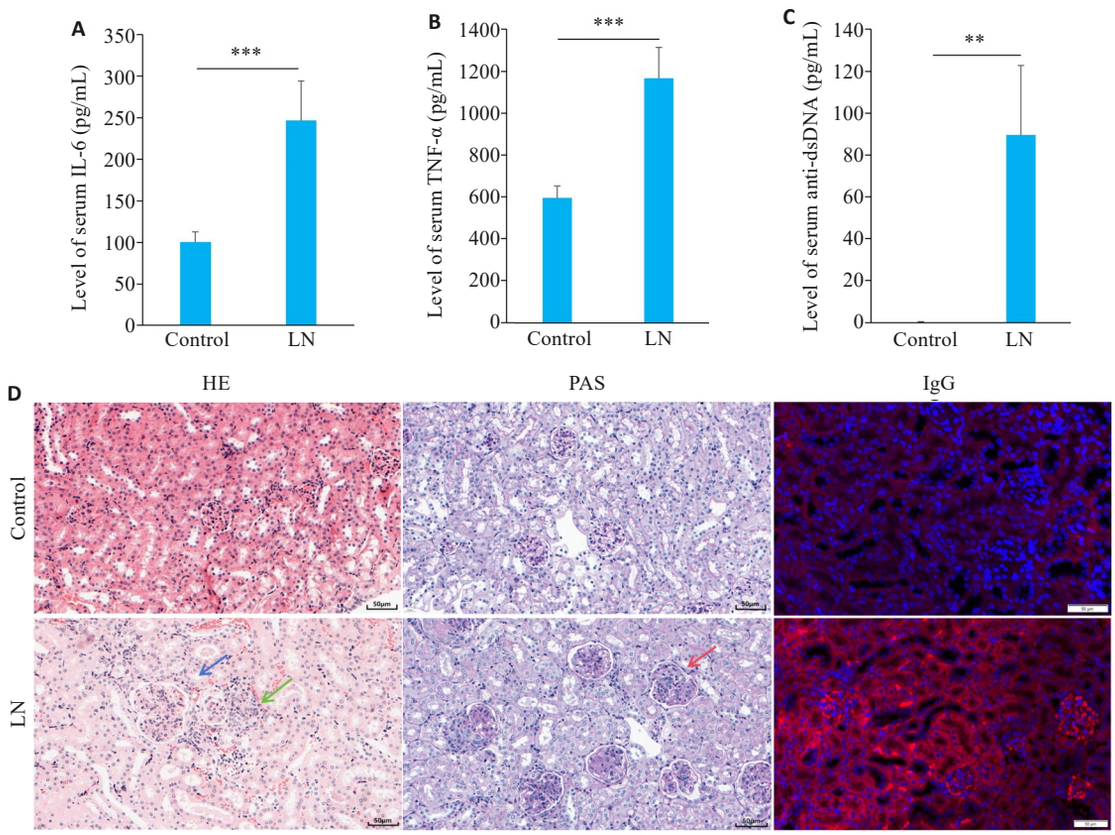

图4 LN小鼠疾病特征性表现

Fig.4 Disease characteristics in the mouse models of LN. **A**: Serum level of IL-6 in LN and control groups. **B**: Serum level of TNF-α in LN and control groups. **C**: Serum level of anti-dsDNA in LN and control groups. **D**: Renal HE staining, PAS staining and IgG staining showing mesangial cell proliferation (blue arrow), lymphocytes infiltration (green arrow), and basement membrane thickening (red arrow) (scale bar=50 μm). ***P*<0.01, ****P*<0.001.

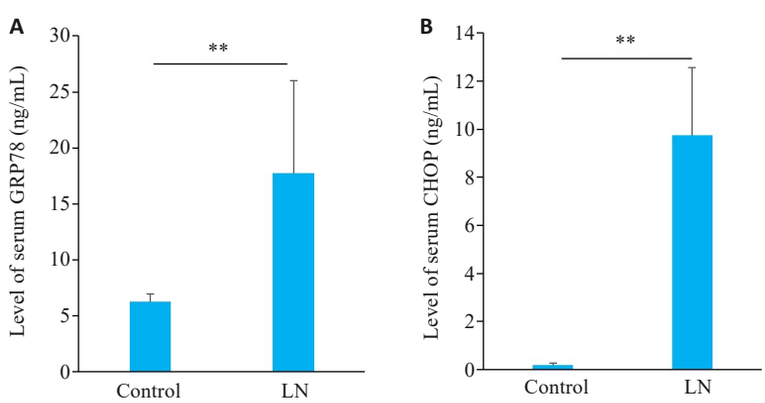

图5 LN小鼠血清GRP78和CHOP水平

Fig.5 Serum levels of GRP78 and CHOP in mouse models of LN. **A**: Serum levels of GRP78 in LN and control groups. **B**: Serum levels of CHOP in LN and control groups. ***P*<0.01.

GRP78和CHOP含量也增加。该现象提示PERK/ATF4/CHOP和IRE1α/JNK/CHOP通路诱导的凋亡可能是LN肾脏驻留细胞损伤的原因，而血清游离GRP78是该现象的可能标志物。与该结果相似的是，先前有报道提示GRP78水平与肾小管细胞损伤有关[26, 27]，提示其下游ERS通路激活[28]，也能侧面支持本研究的观点。ERS诱导的细胞凋亡是由多个信号通路以网络形式调控，如PERK磷酸化可促进ATF4转录，上调CHOP表达，CHOP过表达可促进活性氧生成和蛋白毒性增强，引起异常细胞凋亡[7, 29, 30]；而IRE1α磷酸化可与TRAF2、ASK1形成三聚体进一步激活JNK、CHOP和促凋亡因子Bax，并下调抗凋亡基因Bcl-2，引发线粒体介导的经典细胞凋亡[21, 25, 31]。

综上所述，本研究主要探究GRP78和CHOP在LN

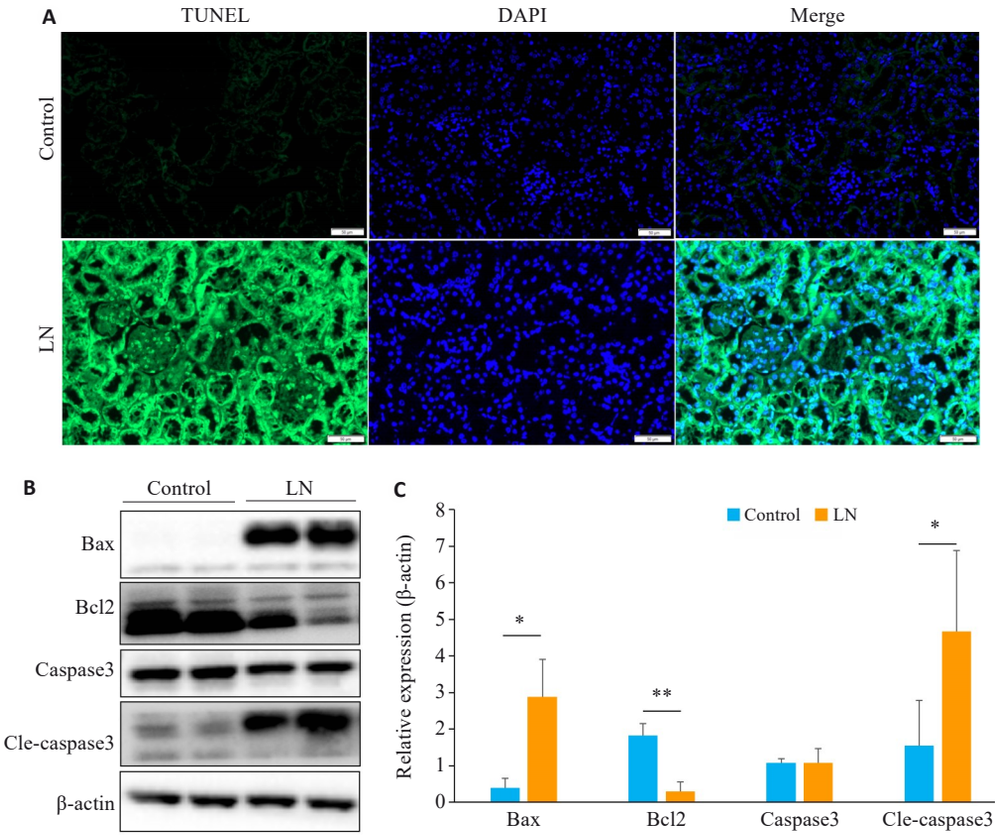

图6 LN小鼠肾脏凋亡增加

Fig.6 Renal apoptosis is increased in mouse models of LN. **A**: Kidney TUNEL staining in LN and control groups (scale bar=50 μm). **B**: Expression of apoptosis-related proteins in LN and control groups. **C**: Relative expression levels of apoptosis-related proteins in the two groups. **P*<0.05, ***P*<0.01.

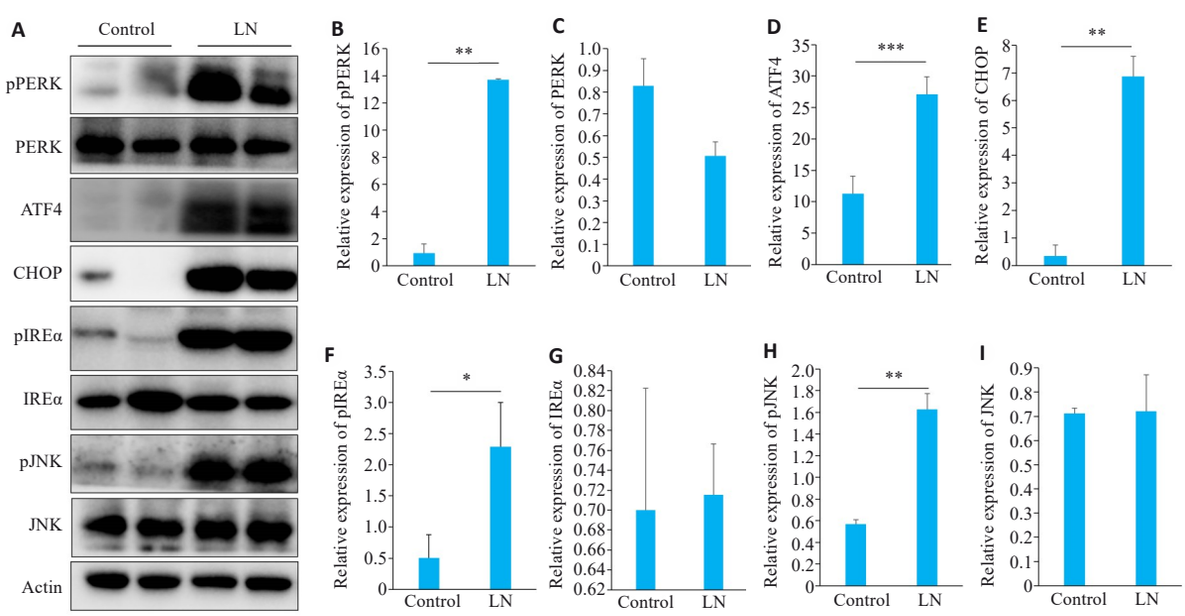

图7 LN小鼠肾脏ERS凋亡相关蛋白表达

Fig.7 Expressions of proteins related to endoplasmic reticulum stress apoptosis in the kidney of LN mice. **A**: Protein bands in Western blotting of endoplasmic reticulum stress-related proteins. **B**-**I**: Relative PERK phosphorylation level and relative expression levels of PERK, ATF4, CHOP, IREα, IREα, phosphorylated JNK, and JNK, respectively. **P*<0.05, ***P*<0.01, ****P*<0.001.

患者血清中表达的变化、临床意义和该变化提示的肾损伤病理机制，即肾驻留细胞可能存在由PERK/ATF4/CHOP和IRE1α/JNK/CHOP双通路介导的ERS凋亡。但在LN中，该通路如何具体调控细胞凋亡，以及影响哪一类肾驻留细胞还有待进一步探究。同时，本研究检测的LN患者样本量较少，未来的研究会进一步扩大样本量并增加取样的时间节点，验证GRP78作为诊断标志物的价值并探究其对LN活动的预测能力。

Declaration of interests: The authors declare no competing interests.

参考文献：

[1] Siegel CH, Sammaritano LR. Systemic lupus erythematosus: a review[J]. JAMA, 2024, 331(17): 1480-91.

[2] Gasparotto M, Gatto M, Binda V, et al. Lupus nephritis: clinical presentations and outcomes in the 21st century[J]. Rheumatology (Oxford), 2020, 59(Suppl5): v39-51.

[3] Anders HJ, Saxena R, Zhao M-H, et al. Lupus nephritis[J]. Nat Rev Dis Primers, 2020, 6: 7.

[4] Marciniak SJ, Chambers JE, Ron D. Pharmacological targeting of endoplasmic reticulum stress in disease[J]. Nat Rev Drug Discov, 2022, 21(2): 115-40.

[5] Celik C, Lee SYT, Yap WS, et al. Endoplasmic reticulum stress and lipids in health and diseases[J]. Prog Lipid Res, 2023, 89: 101198.

[6] Ke H, Su XZ, Dong CT, et al. Sigma-1 receptor exerts protective effects on ameliorating nephrolithiasis by modulating endoplasmic reticulum-mitochondrion association and inhibiting endoplasmic reticulum stress-induced apoptosis in renal tubular epithelial cells [J]. Redox Rep, 2024, 29(1): 2391139.

[7] Cybulsky AV. Endoplasmic reticulum stress, the unfolded protein response and autophagy in kidney diseases[J]. Nat Rev Nephrol, 2017, 13(11): 681-96.

[8] Ibrahim IM, Abdelmalek DH, Elfiky AA. GRP78: a cell's response to stress[J]. Life Sci, 2019, 226: 156-63.

[9] Akinyemi AO, Simpson KE, Oyelere SF, et al. Unveiling the dark side of glucose-regulated protein 78 (GRP78) in cancers and other human pathology: a systematic review[J]. Mol Med, 2023, 29 (1): 112.

[10] Xu ZH, Bu YW, Chitnis N, et al. miR-216b regulation of c-Jun mediates GADD153/CHOP-dependent apoptosis[J]. Nat Commun, 2016, 7: 11422.

[11] Gong QM, Lai TF, Liang LD, et al. Targeted inhibition of CX3CL1 limits podocytes ferroptosis to ameliorate cisplatin-induced acute kidney injury[J]. Mol Med, 2023, 29(1): 140.

[12] Sun MM, Wang FQ, Li HP, et al. Maresin-1 attenuates sepsis-associated acute kidney injury *via* suppressing inflammation, endoplasmic reticulum stress and pyroptosis by activating the AMPK/SIRT3 pathway[J]. J Inflamm Res, 2024, 17: 1349-64.

[13] Andrade-Silva M, Dhillon P, Sanchez-Navarro A, et al. The critical role of endoplasmic reticulum stress and the stimulator of interferon genes (STING) pathway in kidney fibrosis[J]. Kidney Int, 2025, 107 (2): 302-16.

[14] Li HY, Huang LF, Huang XR, et al. Endoplasmic reticulum stress in systemic lupus erythematosus and lupus nephritis: potential therapeutic target[J]. J Immunol Res, 2023, 2023: 7625817.

[15] Yu F, Haas M, Glassock R, et al. Redefining lupus nephritis: clinical implications of pathophysiologic subtypes[J]. Nat Rev Nephrol, 2017, 13(8): 483-95.

[16] Mejia-Vilet JM, Malvar A, Arazi A, et al. The lupus nephritis management renaissance[J]. Kidney Int, 2022, 101(2): 242-55.

[17] Porter AW, Brodsky JL, Buck TM. Emerging links between endoplasmic reticulum stress responses and acute kidney injury[J]. Am J Physiol Cell Physiol, 2022, 323(6): C1697-703.

[18] Chen XY, Shi CR, He MH, et al. Endoplasmic reticulum stress: molecular mechanism and therapeutic targets[J]. Signal Transduct Target Ther, 2023, 8(1): 352.

[19] Gallazzini M, Pallet N. Endoplasmic reticulum stress and kidney dysfunction[J]. Biol Cell, 2018, 110(9): 205-16.

[20] Hetz C, Zhang KZ, Kaufman RJ. Mechanisms, regulation and functions of the unfolded protein response[J]. Nat Rev Mol Cell Biol, 2020, 21(8): 421-38.

[21] Zhang RJ, Bian C, Gao J, et al. Endoplasmic reticulum stress in diabetic kidney disease: adaptation and apoptosis after three UPR pathways[J]. Apoptosis, 2023, 28(7/8): 977-96.

[22] Kapuy O. Mechanism of decision making between autophagy and apoptosis induction upon endoplasmic reticulum stress[J]. Int J Mol Sci, 2024, 25(8): 4368.

[23] Verfaillie T, Rubio N, Garg AD, et al. PERK is required at the ER-mitochondrial contact sites to convey apoptosis after ROS-based ER stress[J]. Cell Death Differ, 2012, 19(11): 1880-91.

[24] Chen S, Li X, Zhang XW, et al. PCV2 and PRV coinfection induces endoplasmic reticulum stress *via* PERK-eIF2α -ATF4-CHOP and IRE1-XBP1-EDEM pathways[J]. Int J Mol Sci, 2022, 23(9): 4479.

[25] Cao Y, Hu LT, Chen RK, et al. Unfolded protein response-activated NLRP3 inflammasome contributes to pyroptotic and apoptotic podocyte injury in diabetic kidney disease *via* the CHOP-TXNIP axis [J]. Cell Signal, 2025, 130: 111702.

[26] Nakatsuka A, Yamaguchi S, Jun WD. GRP78 contributes to the beneficial effects of SGLT2 inhibitor on proximal tubular cells in DKD[J]. Diabetes, 2024, 73(5): 763-79.

[27] Trink J, Ahmed U, O'Neil K, et al. Cell surface GRP78 regulates TGFβ1-mediated profibrotic responses *via* TSP1 in diabetic kidney disease[J]. Front Pharmacol, 2023, 14: 1098321.

[28] Jin RB, Zhao AR, Han SY, et al. The interaction of S100A16 and GRP78 actives endoplasmic reticulum stress-mediated through the IRE1α/XBP1 pathway in renal tubulointerstitial fibrosis[J]. Cell Death Dis, 2021, 12(10): 942.

[29] Deng F, Zhang HP, Zhou W, et al. TRPA1 promotes cisplatin-induced acute kidney injury *via* regulating the endoplasmic reticulum stress-mitochondrial damage[J]. J Transl Med, 2023, 21 (1): 695.

[30] Park SJ, Kim Y, Li C, et al. Blocking CHOP-dependent TXNIP shuttling to mitochondria attenuates albuminuria and mitigates kidney injury in nephrotic syndrome[J]. Proc Natl Acad Sci USA, 2022, 119(35): e2116505119.

[31] Lin BB, Zhang XB, Xu XG. Nerve growth factor protects retinal ganglion cells related to inhibiting endoplasmic reticulum stress by inhibiting IRE1-JNK-CHOP signaling pathway[J]. Ocul Immunol Inflamm, 2022, 30(6): 1341-6.

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