Endoplasmic Reticulum Stress in Glomerulonephritis: The Bad Guy Turns Good?

Masanori Kitamura

Department of Molecular Signaling, University of Yamanashi, Chuo, Yamanashi, Japan


The balance between somatic cellular machinery for defense against local effector molecules determines the tissue fate of inflammation—progression or resolution. We previously proposed the concept of glomerular “self-defense” as essential for spontaneous subsidence of glomerular inflammation. A line of evidence supporting this concept is that glomeruli, when faced with activated leukocytes or exposure to pathogenic factors, defend themselves through intrinsic machinery brought into play in resident glomerular cells. For example, in glomeruli isolated from the regeneration phase of anti-Thy 1 GN, induction of inflammatory genes is blunted in vitro. When activated macrophages are adoptively transferred into the nephritic glomeruli, ex vivo induction of chemokines is also suppressed compared with the induction produced by normal glomeruli. Kawachi et al. also provides in vivo evidence. In an acute model of anti-Thy 1 GN, macrophages accumulate within 24 h and peak at 1 wk. However, when Thy 1 inflammation is reinduced 2 wk after the first administration of anti-Thy 1 antibody, accumulation of macrophages is suppressed. These results indicate the possibility that, once activated, glomerular cells acquire a tolerance against subsequent exposure to inflammatory stimuli.

Under inflammatory conditions, various molecules are induced by activation of NF-κB, something that is also observed in various glomerulonephritides. Previously we reported that mesangial cells activated by bystander macrophages show a blunted engagement of NF-κB in response to subsequent macrophage exposure. In vivo priming of mesangial cells by activated macrophages in glomeruli also induce tolerance in mesangial cells. Macrophage-derived soluble factors may be responsible for this induction of mesangial cell tolerance. These data suggest that glomerular cells, once exposed to an inflammatory environment, become insensitive to subsequent reactivation by proinflammatory stimuli. However, molecular mechanisms underlying this phenomenon are unclear.

Recently, Inagi et al. reported that preconditioning of kidneys to endoplasmic reticulum (ER) stress attenuates development of anti-Thy1 GN. Induction of ER stress is observed in isolated nephritic glomeruli, especially in glomerular epithelial and mesangial cells. Pretreatment of rats with ER stress inducers markedly ameliorates the manifestations of disease, including cell proliferation and proteinuria. ER stress may be induced by various inflammatory mediators including cytokines, reactive oxygen/nitrogen species, and complement, and the insensitivity of nephritic glomeruli to inflammatory stimuli may be ascribed to induction of ER stress.

ER stress is defined as the accumulation of unfolded or misfolded proteins in the ER, which triggers an adaptive program called the unfolded protein response (UPR). The UPR alleviates ER stress by suppression of protein synthesis, facilitation of protein folding, and reinforced degradation of unfolded proteins. ER stress is implicated in a wide range of pathologies, including inflammatory diseases. For example, systemic inflammation caused by LPS results in ER stress in various murine organs. ER stress is also induced by renal inflammation, intestinal inflammation, and autoimmune disorders, indicating a possible link between ER stress and inflammatory events. Indeed, several investigators suggest the potential of ER stress for activation of NF-κB and consequent induction of inflammation, as reviewed by Zhang and Kaufman. For example, ER stress inducers including tunicamycin, brefeldin A, 2-deoxyglucose, and thapsigargin increase activity of NF-κB as well as NF-κB-dependent gene expression. The mechanisms underlying the proinflammatory potential of ER stress have not been fully elucidated, but the TRAF2 (TNF-receptor-associated factor 2)/IRE1 (inositol-requiring kinase 1) pathway, the PERK (double-stranded RNA-activated protein kinase-like ER kinase) - eIF2α (eukaryotic translation initiation factor 2α) pathway, and/or the ATF6 (activating transcription factor 6) - Akt pathway may mediate its proinflammatory actions, as I reviewed recently.

Because of the weight of these observations, the
proinflammatory aspect of ER stress has been of one-sided interest to date.14,16

However, ER stress and the UPR mirror the Janus faces. We recently observed that preceding ER stress responses blunt subsequent activation of NF-κB by inflammatory cytokines in several renal cells. For example, in podocytes, mesangial cells, and tubular cells stimulated by TNFα, the expression of NF-κB-dependent genes (e.g., monocyte chemoattractant protein 1 and inducible nitric oxide synthase) is abrogated by pretreatment with several UPR-inducible, anti-inflammatory agents, including cyclopentine A, FK506, indomethacin, K-7174, and geranylgeranlactone.17–20 Induction of the UPR by other inducers also reproduces the suppression of NF-κB and NF-κB-dependent gene expression.21 Although ER stress triggers activation of NF-κB in the early phase, these results indicate a possibility that a subsequent UPR has the potential to inhibit activation of NF-κB in a later phase. Molecular mechanisms involved in this negative regulation of NF-κB by the UPR have not been fully elucidated, but there are several possibilities; that is, ER stress-induced UPR may inhibit NF-κB by downregulating TRAF2 (TNF receptor-associated factor 2) and/or the induction of C/EBPs (CCAAT/enhancer-binding proteins) A20.17,18,21 Using subtilase cytotoxin (SubAB), a selective inducer of ER stress, we have evidence that treatment of cells with SubAB causes ER stress and acute activation of NF-κB with a peak at 6 to 12 h, whereas this activation subsides within 24 h.22 Thereafter, target cells become insensitive to inflammatory cytokines and exhibit blunted activation of NF-κB.17

It is worthwhile to note that the anti-inflammatory potential of ER stress may not only be on resident cells but also on inflammatory macrophages. Recently, we reported pretreatment of macrophages with SubAB triggers the UPR and inhibits LPS-induced activation of NF-κB as well as production of inflammatory mediators, including monocyte chemoattractant protein 1 and TNF-α.23 Consistent with this finding, administration of a sublethal dose of SubAB induces a UPR that protects mice from LPS-induced endotoxic lethality and LPS-triggered arthritis.23

Taken together, the current data summarized here propose a biphasic, bidirectional regulation of NF-κB by ER stress during the course of glomerular inflammation. Although ER stress activates NF-κB in the early phase, the subsequent UPR suppresses inflammatory responses in a later phase. During inflammation, the adaptive UPR eventually turns anti-inflammatory, which may play a role in glomerular self-defense. ER stress is possibly involved in the initiation of inflammation and in its resolution.

DISCLOSURES
None.

REFERENCES
15. Pahl HL, Baueierle PA: A novel signal transduction pathway from the endoplasmic reticulum to the nucleus is mediated by transcription factor NF-κB. EMBO J 14: 2580–2588, 1995