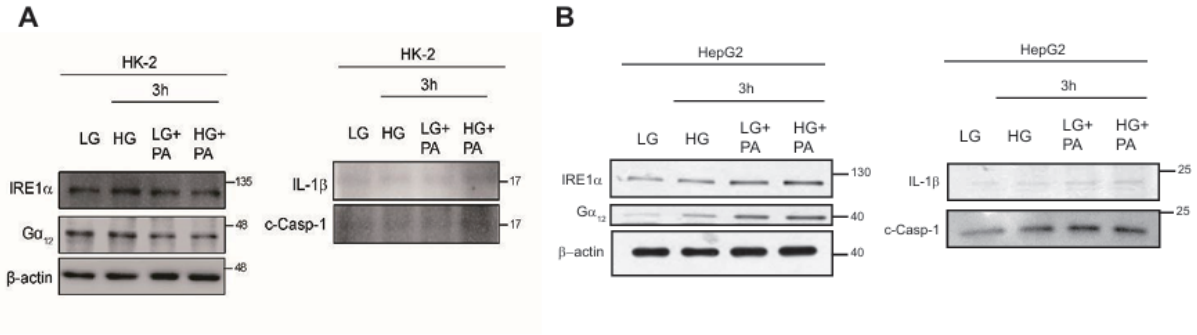
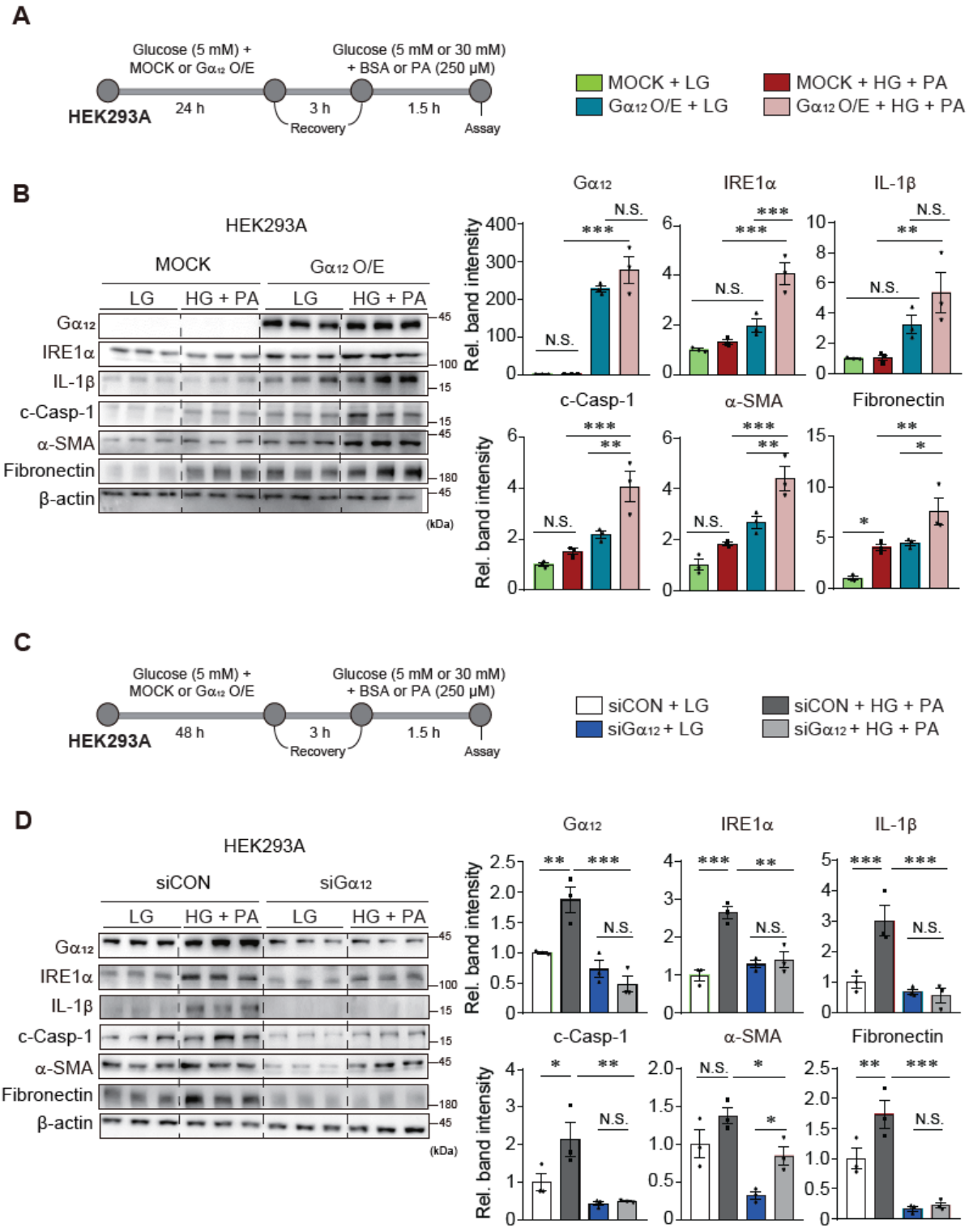
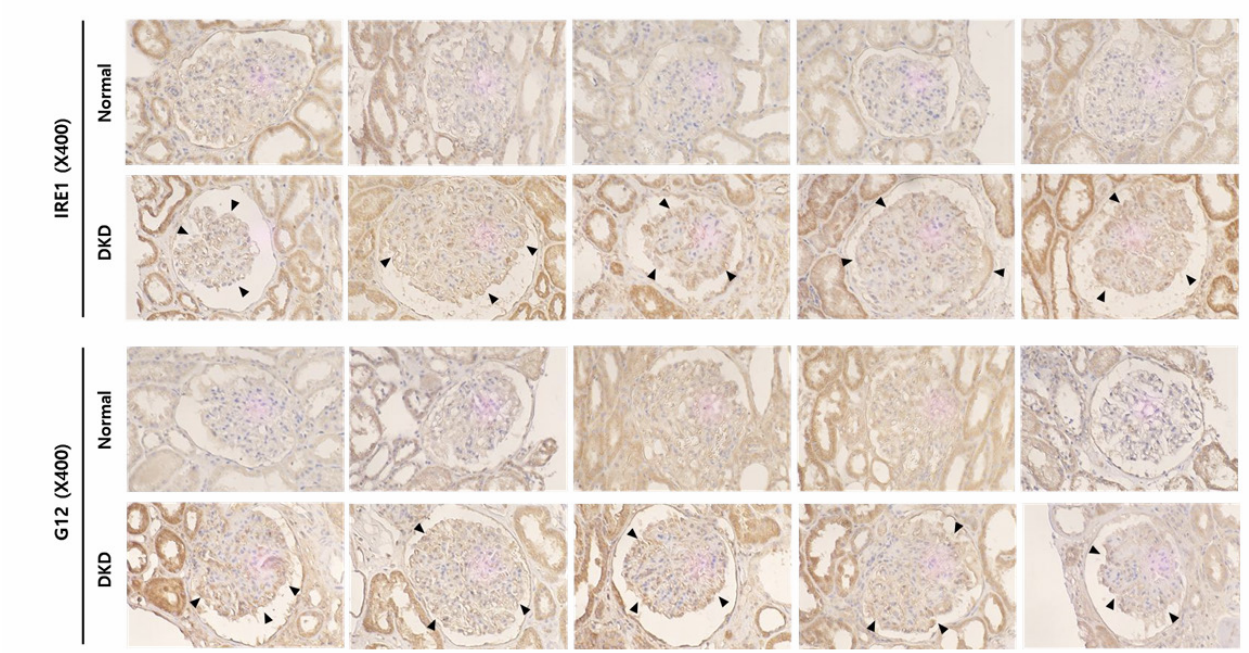


Supplementary Figure 1. Effects of HG and/or PA treatments on ER stress and pyroptosis markers in HK-2 **(A)** or HepG2 cells **(B)**.



Supplementary Figure 2. Effect of $G\alpha_{12}$ overexpression or knockdown on ER stress-, pyroptosis-, and fibrosis-associated proteins in HEK293A cells treated with HG plus PA

(A) Schematic illustration of $G\alpha_{12}$ overexpression experiment in HEK293A cells. **(B)** Immunoblots of $G\alpha_{12}$, IRE1α, IL-1β, c-Casp, fibronectin and α-SMA in HEK293A cells transfected with a $G\alpha_{12}$-encoding plasmid or MOCK, and subsequently exposed to high glucose and palmitic acid (HG+PA) (n = 3 each). **(C)** Experimental scheme depicting $G\alpha_{12}$ siRNA knockdown experiment in HEK293A cells. **(D)** Immunodetection assays in the cells treated with HG+PA after transfection with siRNA targeting $G\alpha_{12}$ or control siRNA (siCon) (n = 3 each). Values are represented as mean ± SEM (*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, and N.S., not significant). One-way ANOVA in association with a Tukey's multiple comparison was done to assess statistical significance (**B, D**).



Supplementary Figure 3. Immunostaining of human kidney morphologies. Shown above are representative images from the tissue samples of normal individuals and DKD patients (n = 4 for normal vs. n = 10 for DKD). Arrowheads indicate the regions of either IRE1 or $G\alpha_{12}$ overexpression.