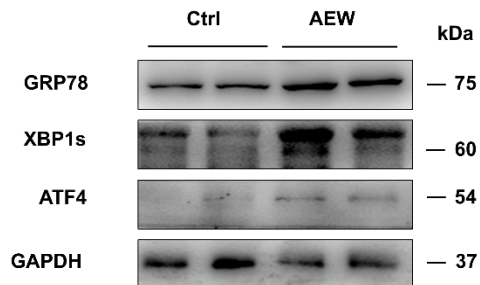
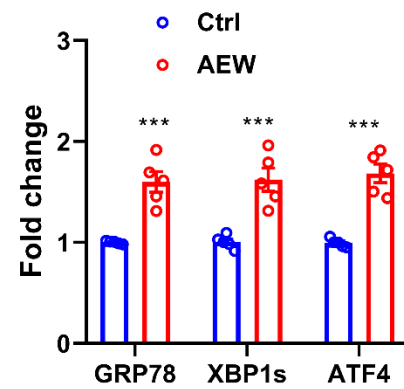


Supplementary Materials

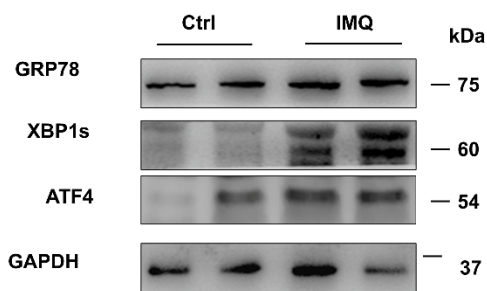
A



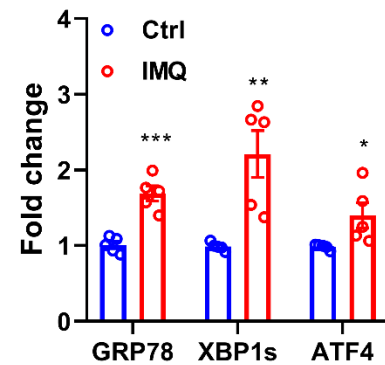
B



C

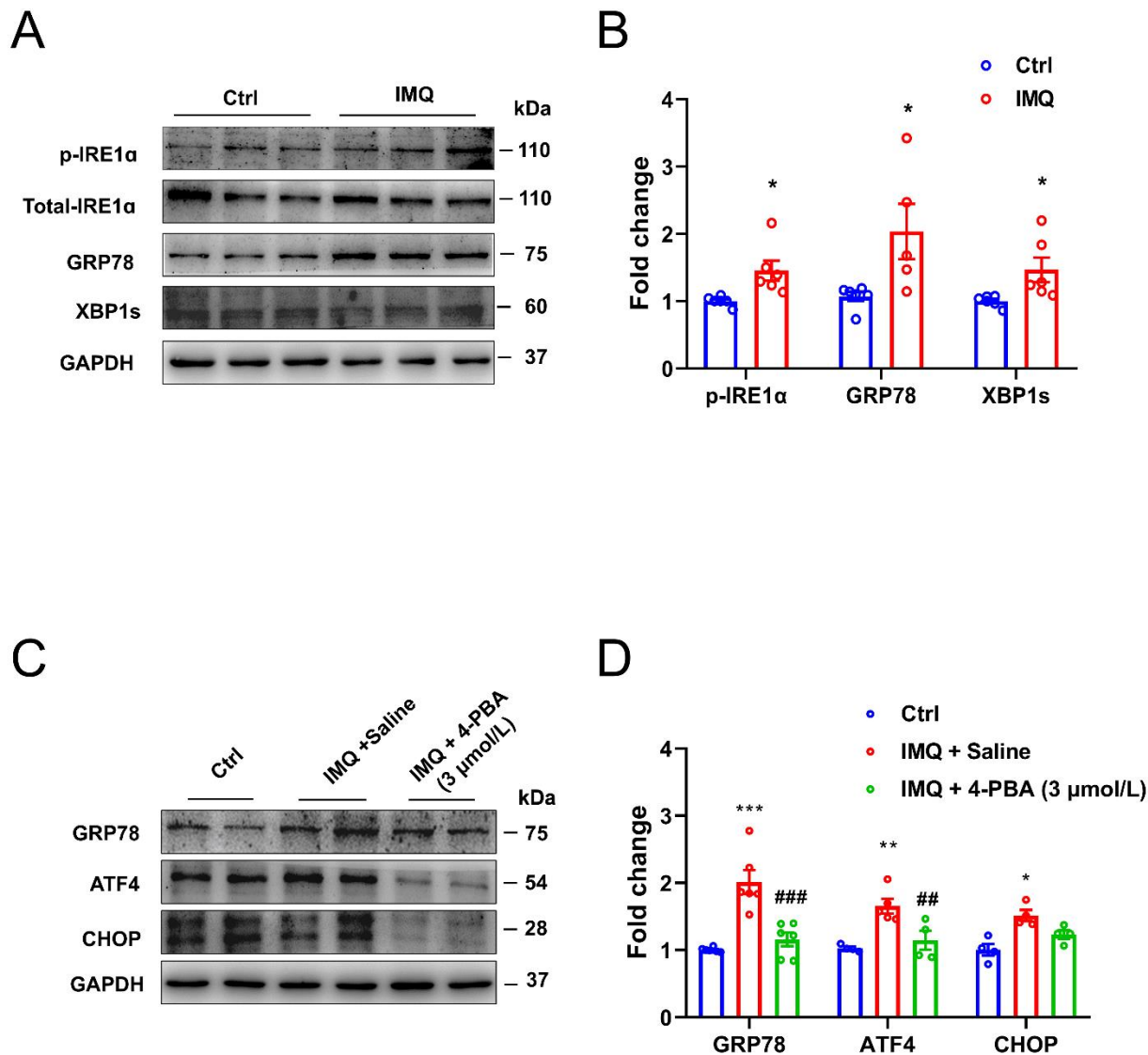


D

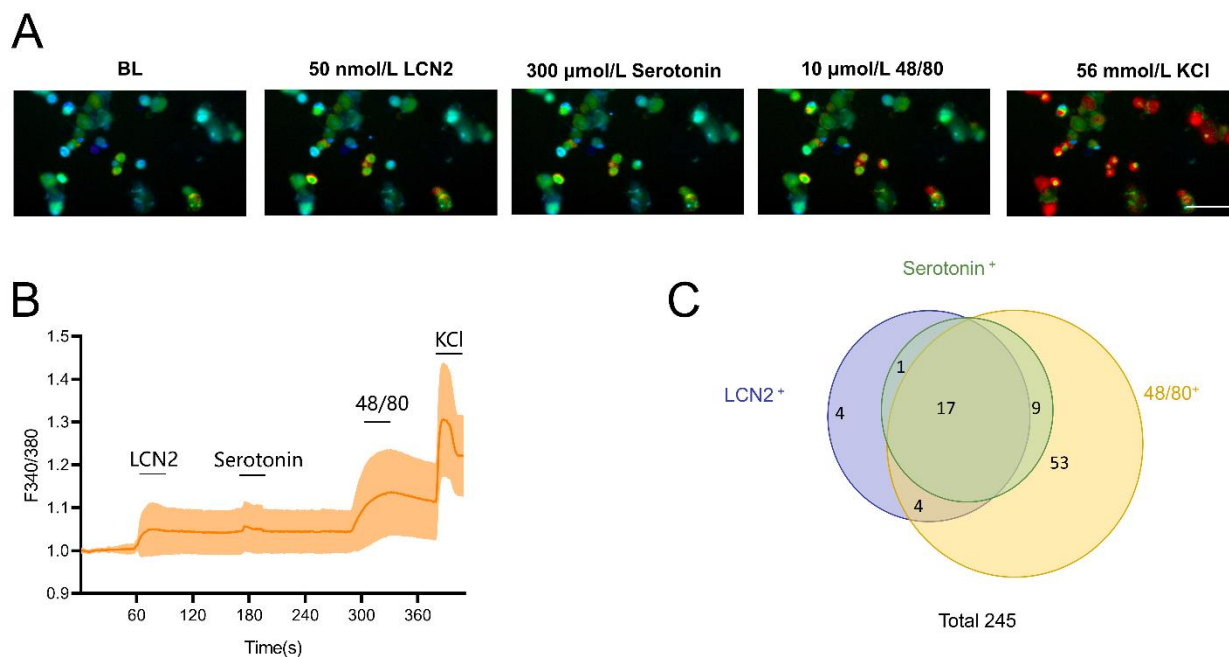


Supplementary Fig. S1 ER stress-related proteins are activated in the skin of chronic itch models.

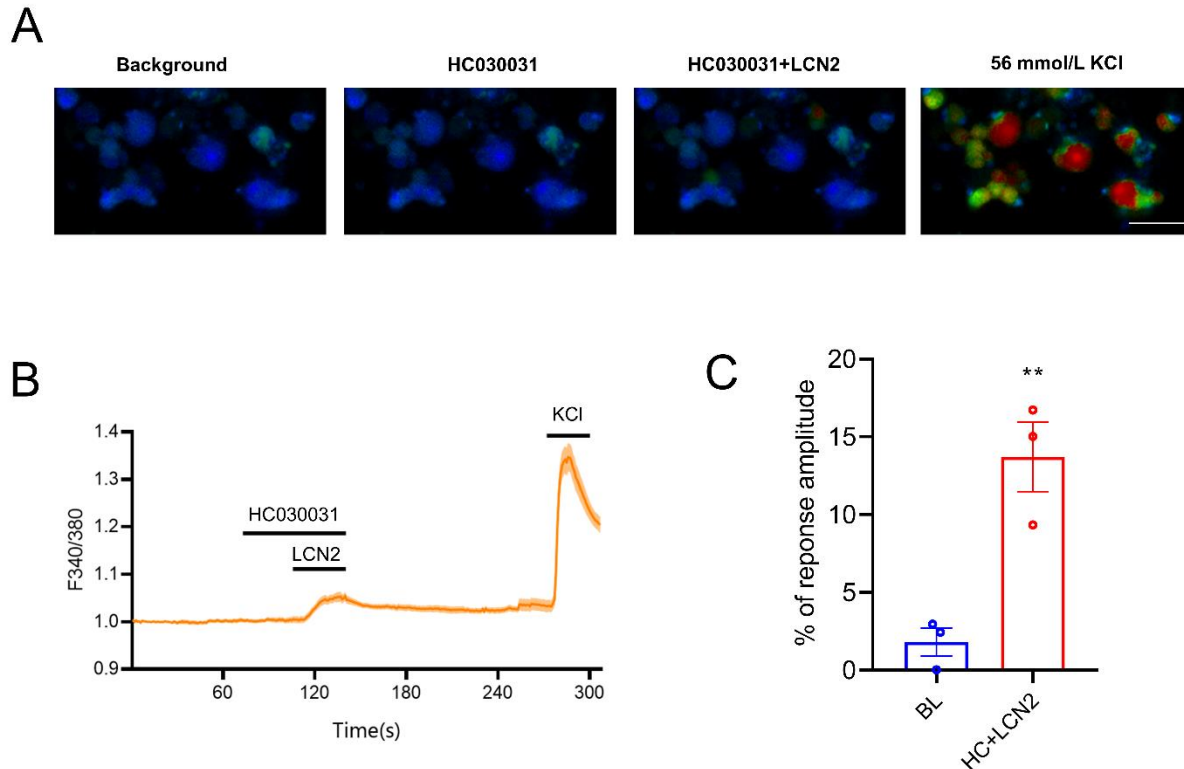
A, B Representative western blot images and quantification of ER stress-related proteins GRP78, XBP1s, and ATF4 in the affected skin treated with AEW, respectively. **C, D** Representative western blot images and quantification of ER stress-related proteins GRP78, XBP1s, and ATF4 in the affected skin treated with imiquimod, respectively ($n = 5$, *** $P < 0.001$, multiple t tests).



Supplementary Fig. S2 ER stress-related proteins are activated in imiquimod-treated HaCaT cells in vitro. **A, B** Representative western blot images and quantification of ER stress-related proteins p-IRE1α, GRP78, and XBP1s in HaCaT cells with or without the treatment of imiquimod, respectively ($n = 5-6$, $*P < 0.05$ vs Ctrl, multiple t tests). **C, D** The effect of 4-PBA on the expression of ER stress-related proteins GRP78, ATF4, and CHOP, respectively ($n = 4-6$, $*P < 0.05$, $**P < 0.01$, $***P < 0.001$ vs Ctrl, $##P < 0.01$, $###P < 0.001$ vs IMQ + saline, one-way ANOVA following Bonferroni's test).



Supplementary Fig. S3 LCN2, serotonin, and compound 48/80 evoked calcium signaling in DRG neurons. **A** Representative images of DRG neurons responding to recombinant LCN2, serotonin, and compound 48/80. **B** Median trace of Ca^{2+} transients of DRG neurons pre- and post- LCN2, serotonin, and compound 48/80 perfusion ($n = 98$, median $\pm$ 95%CI). **C** Cell distribution and overlapping activated by LCN2, serotonin, and compound 48/80.



Supplementary Fig. S4 The effect of HC030031, the antagonist of TRPA1, on the LCN2-evoked calcium signaling in DRG neurons. **A** The representative images of DRG neurons' response to LCN2 in the presence of HC030031. **B** Trace of Ca^{2+} transients of DRG neurons pre- and post- LCN2 in the presence of HC030031. **C** The averaged peak $\Delta F/F$ of calcium activity of DRG neurons in response to LCN2 in the presence of HC030031.

Supplementary Table 1 Primers used in this study

Primer Name	Sequence (5' -> 3')
GAPDH-R	GATGCCAAAGTTGTCATGGA
GAPDH-F	CATTGACCTCAACTACATGG
XBP1s-R	GGCCTGCACCTGCTGCGGACTC
XBP1s-F	GCTTGTGATTGAGAACCAGG
ATF4-R	CATTCGAAACAGAGCATCGA
ATF4-F	GTTGGTCAGTGCCTCAGACA
GRP78-R	GCTGCTGTTGGCTCATTG
GRP78-F	GAAACTGCCGAGGCGTAT

CHOP-R	CTCATTCTCCTGCTCCTTCTCG
CHOP-F	AGAGTGGTCAGTGCGCAGC
LCN2-F	AAGAGCAGAGAGTGAGGAGGACT
LCN2-R	TTCCTGTTGCTCAACCTTGC
TXNIP-F	AACAACAACCATTTTCCCCGCTAG
TXNIP-R	TTCTCCCATTTGGCTACTTGGCC
