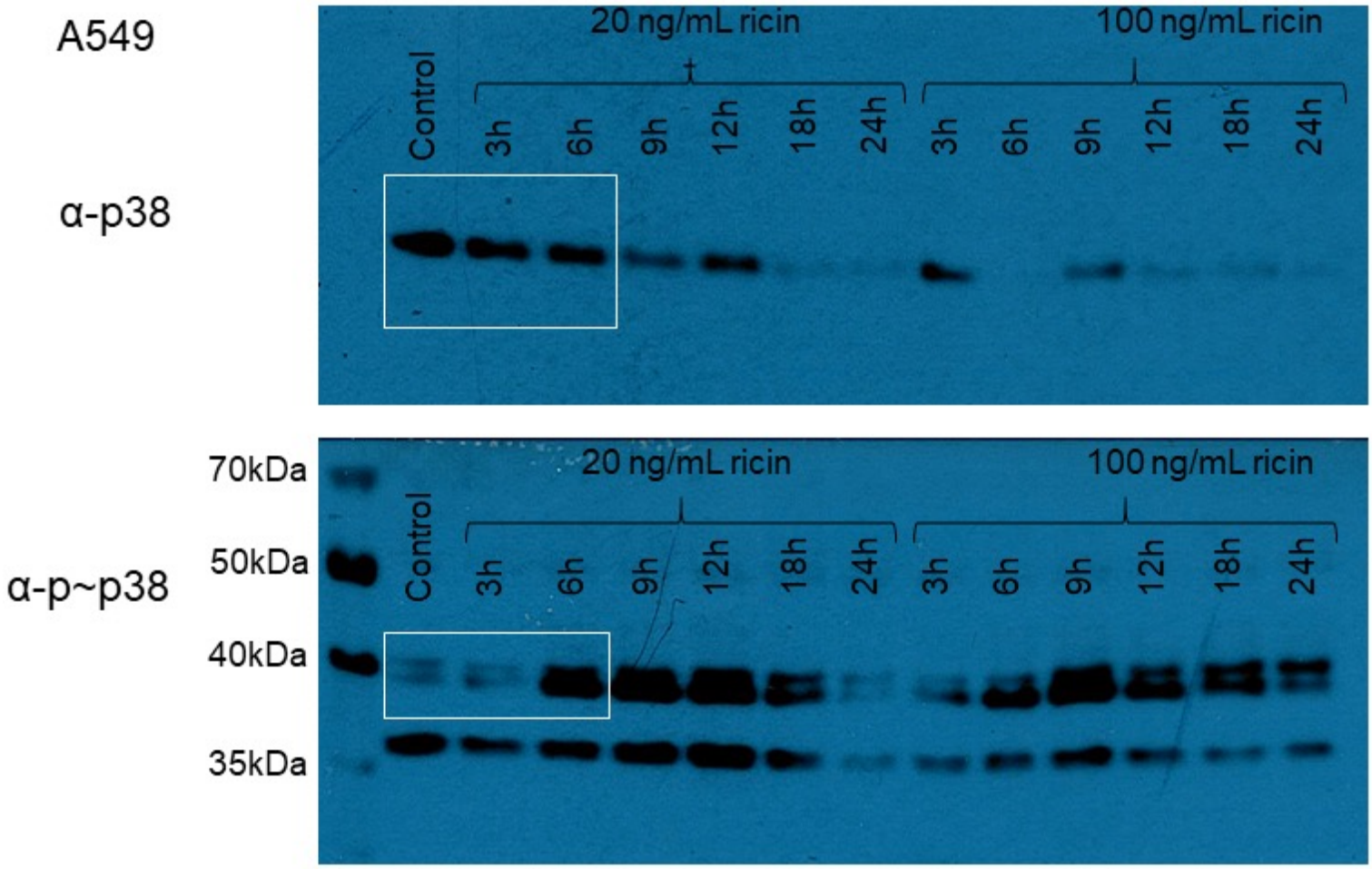
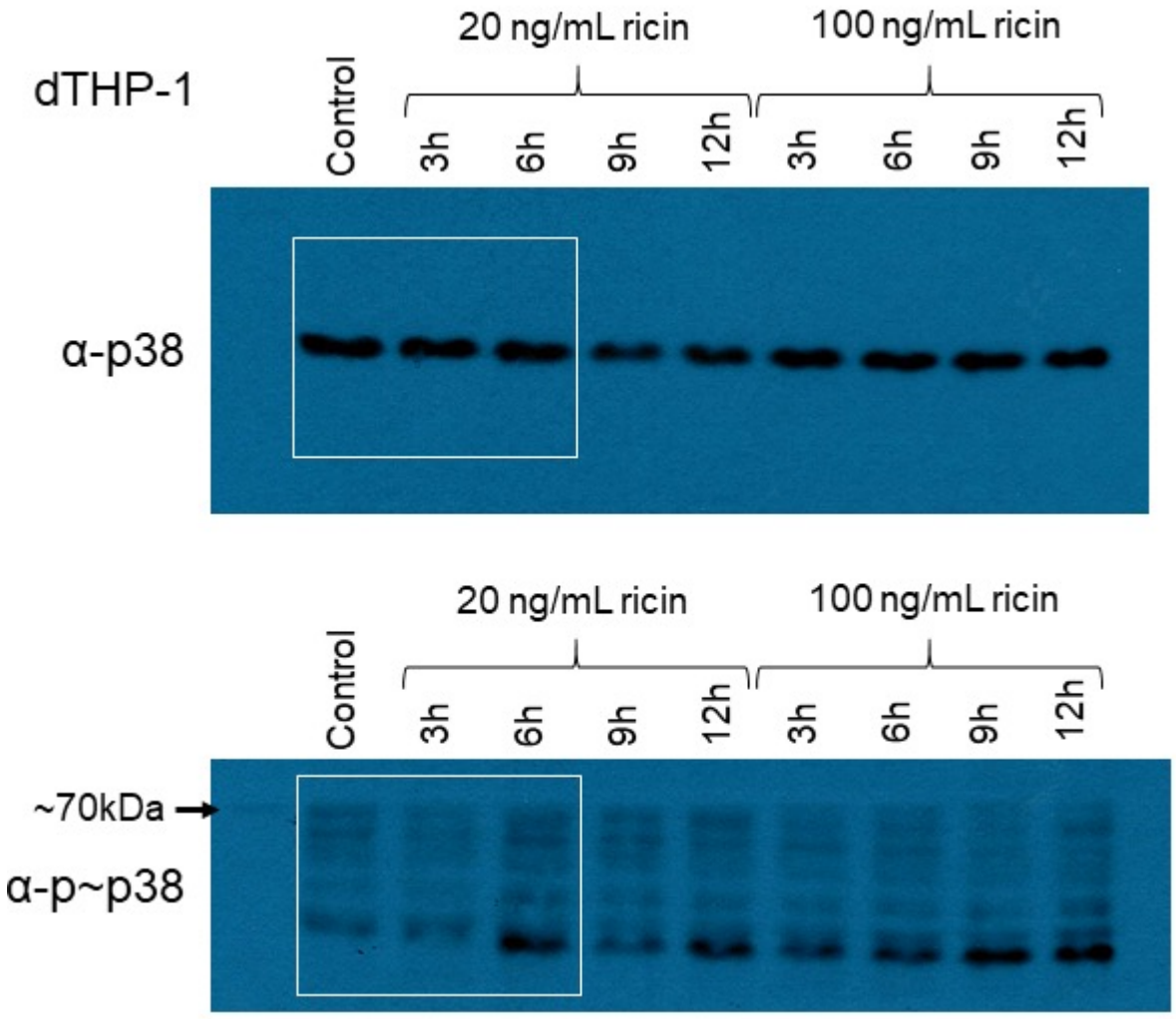
Supplemental Figure 1



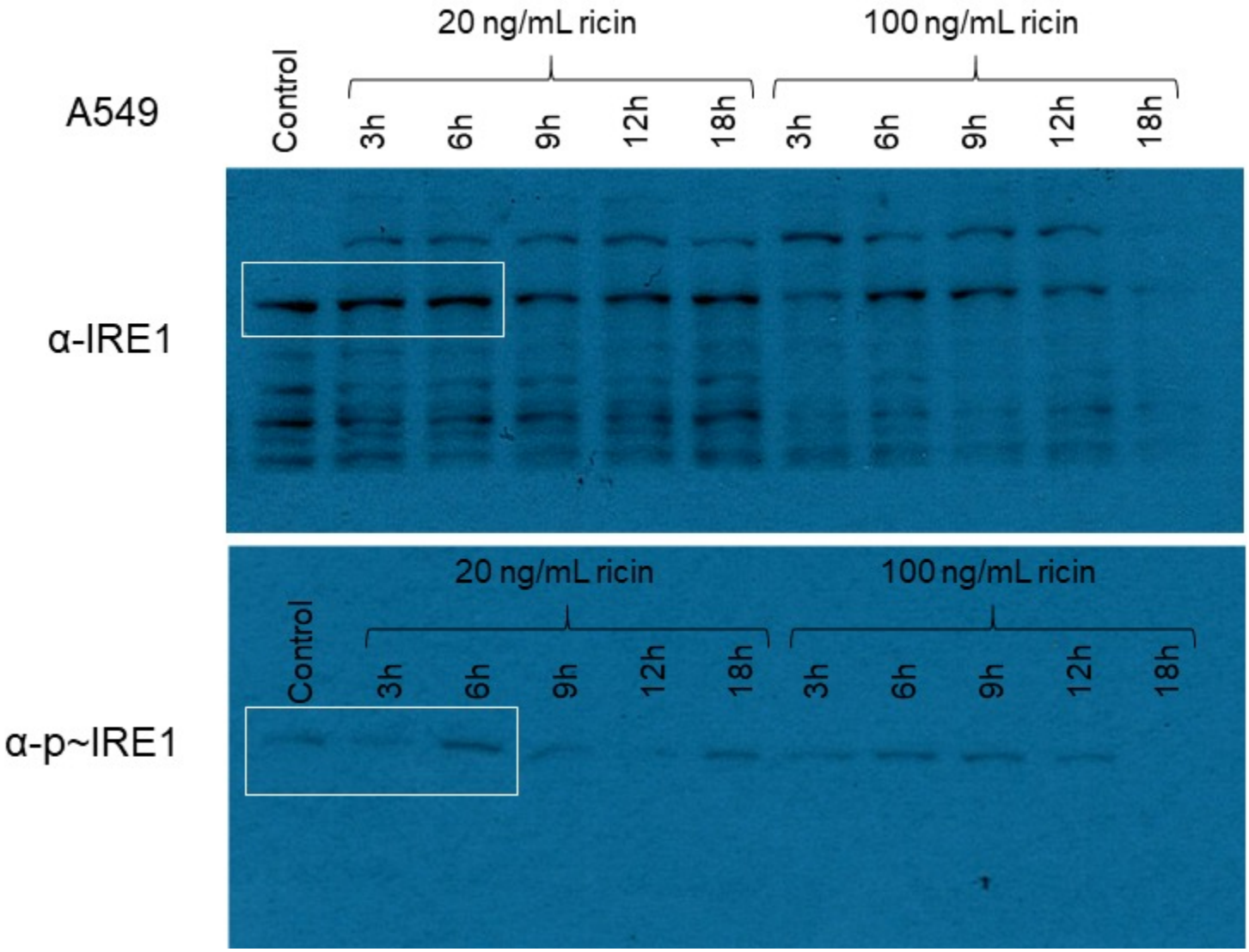
Supplemental Figure 1: A549 cell p38 blot films
Full film areas of membrane swatches probed with anti-p38 and anti-phospho-p38 antibodies. Development with anti-p38 produced a single clear band on a membrane swatch cut just above the ~70 kDa ladder band and just below the 35 kDa ladder band. Development with anti-phospho-p38 produced a doublet band at ~40 kDa, the expected molecular weight of the target protein. An additional single band appeared at ~35 kDa. White boxes indicate the image areas presented in Fig. 1 B.

Supplemental Figure 2



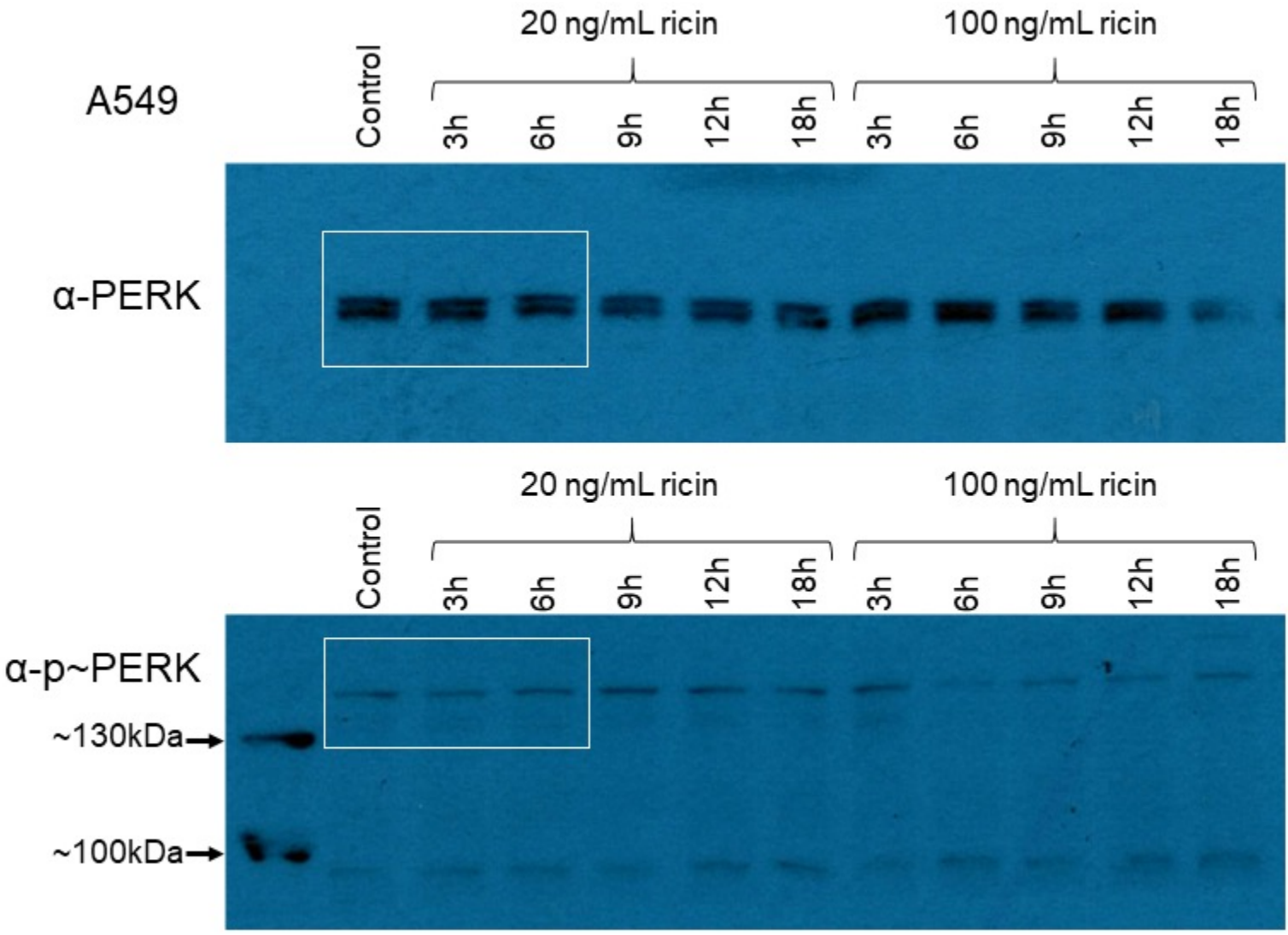
Supplemental Figure 2: dTHP-1 cell p38 blot films
Full film areas of membrane swatches probed with anti-p38 and anti-phospho-p38 antibodies. Development with anti-p38 produced a single clear band on a membrane swatch cut just above the ~70 kDa ladder band and just below the 35 kDa ladder band. Development with anti-phospho-p38 produced a series of faint bands ranging from ~70 kDa to ~40 kDa. White boxes indicate the image areas presented in Fig. 1 C.

Supplemental Figure 3



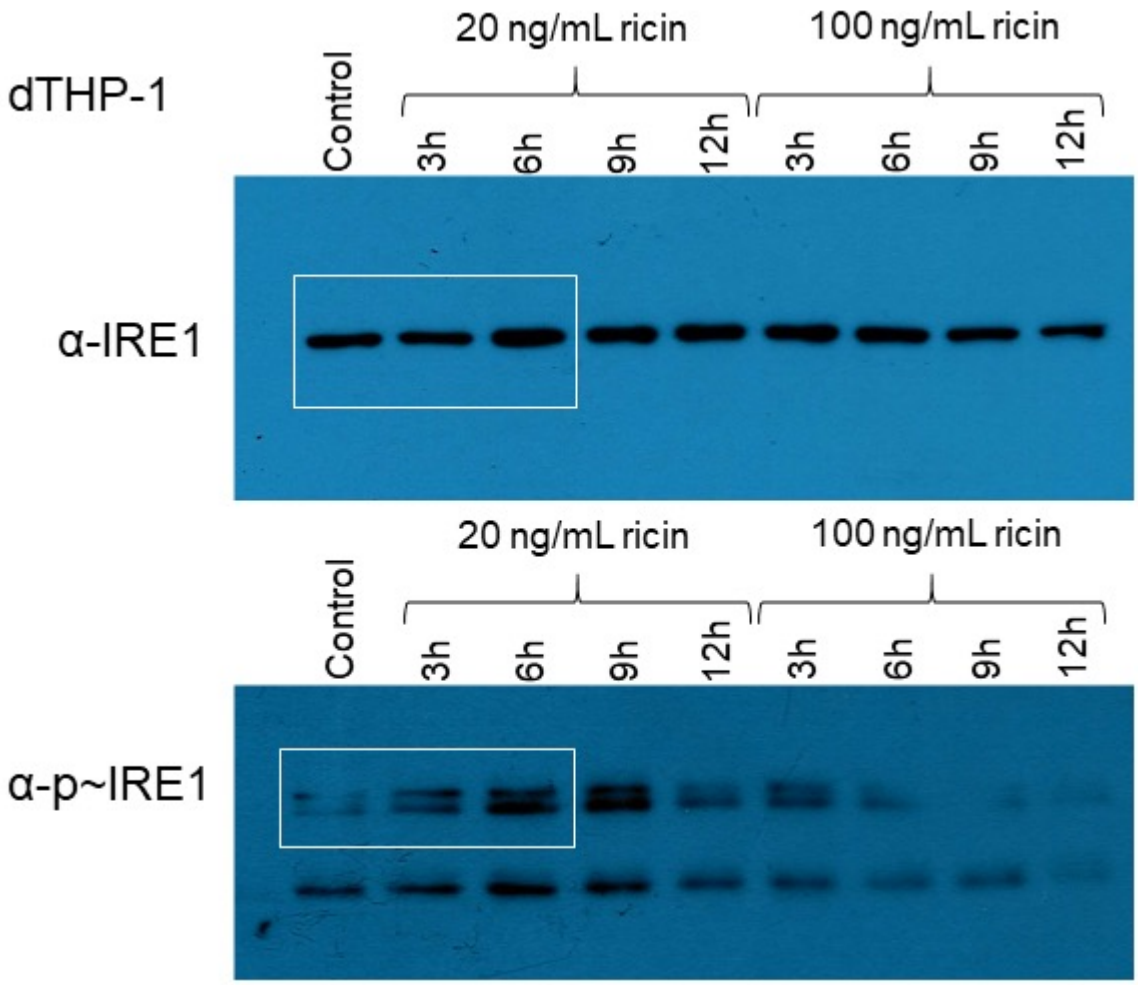
Supplemental Figure 3: A549 cell IRE1 blot films
Full film areas of membrane swatches probed with anti-IRE1 and anti-phospho-IRE1 antibodies. The membrane swatch includes the entire top of the membrane down to a cut made just above the ~70 kDa ladder band. Development with anti-IRE1 produced a number of bands. The band selected for display was closest to the expected molecular weight of ~130 kDa. Development with anti-phospho-IRE1 produced a single faint band. White boxes indicate the image areas presented in Fig. 2 C.

Supplemental Figure 4



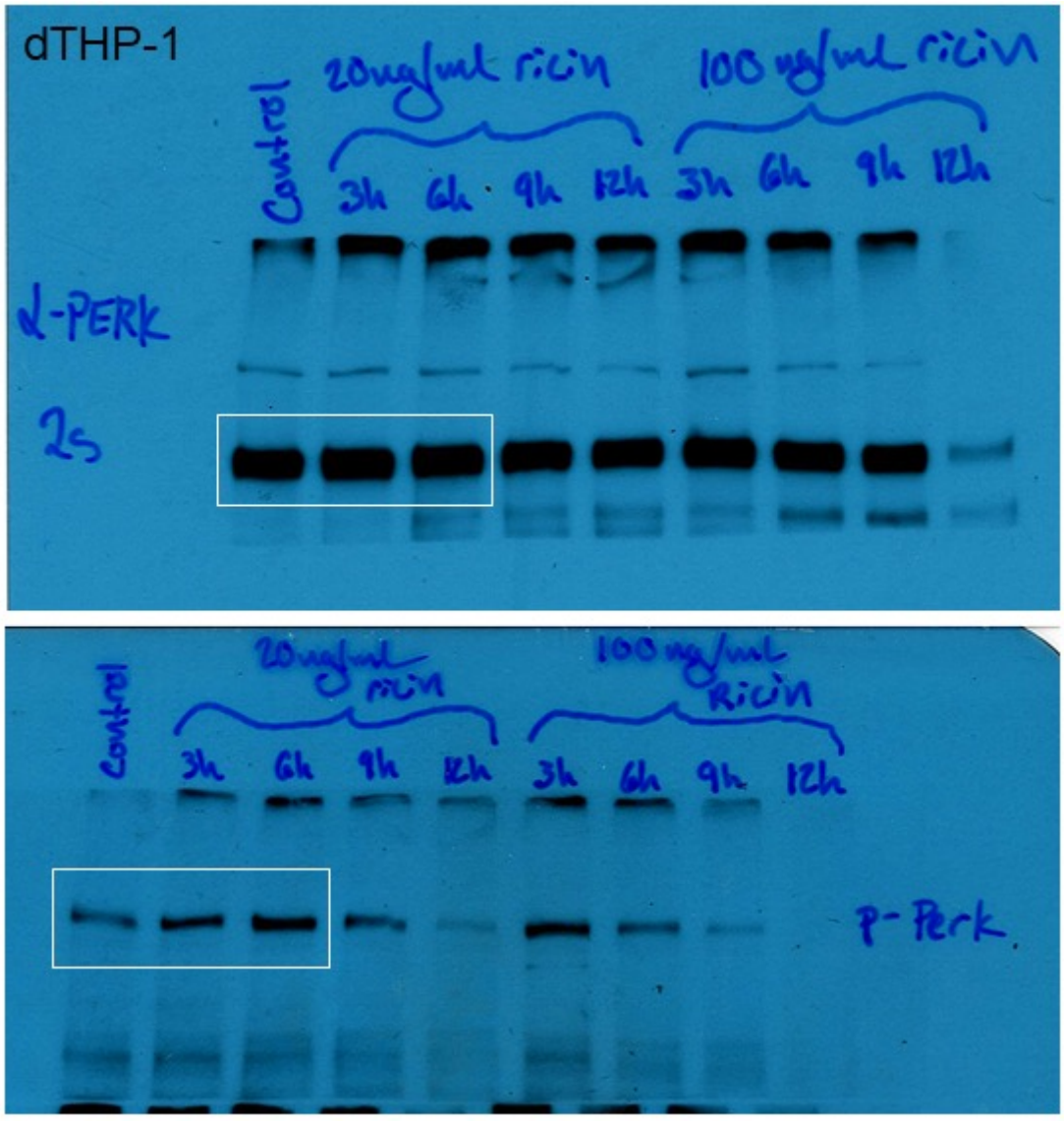
Supplemental Figure 4: A549 cell PERK blot films
Full film areas of membrane swatches probed with anti-PERK and anti-phospho-PERK antibodies. The membrane swatch includes the entire top of the membrane down to a cut made just above the ~70 kDa ladder band. Development with anti-PERK produced only a strong doublet band. Development with anti-phospho-PERK produced two faint bands; one larger than 130 kDa which is closest to the expected size of 170 kDa, and one smaller than ~ 100 kDa. White boxes indicate the image areas presented in Fig. 2 D.

Supplemental Figure 5



Supplemental Figure 5: dTHP-1 cell IRE1 blot films
Full film areas of membrane swatches probed with anti-IRE1 and anti-phospho-IRE1 antibodies. The membrane swatch includes the entire top of the membrane down to a cut made just above the ~70 kDa ladder band. Development with anti-IRE1 produced a single strong band. Development with anti-phospho-IRE1 produced a larger doublet band which was closest to the expected molecular weight of 110 kDa, and a smaller band at the very bottom of the swatch. White boxes indicate the image areas presented in Fig. 2 C.

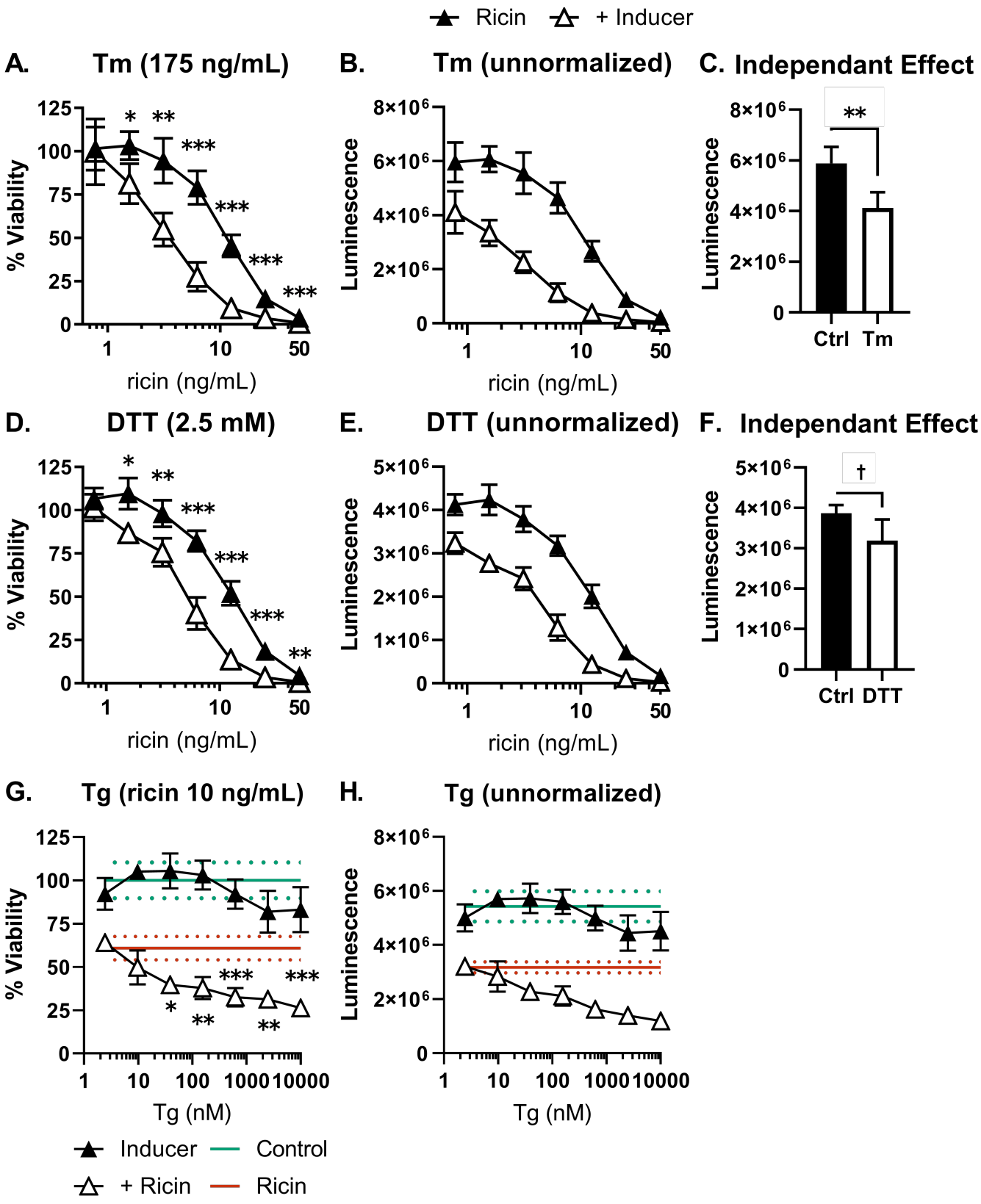
Supplemental Figure 6



Supplemental Figure 6: dTHP-1 cell PERK blot films

Full film areas of membrane swatches probed with anti-PERK and anti-phospho-PERK antibodies. The membrane swatch includes the entire top of the membrane down to a cut made just above the ~70 kDa ladder band. Development with anti-PERK produced a very strong band around the expected size of 140kDa, with smaller products also visible. Development with anti-phospho-PERK produced a clear band in range of the expected size of 170 kDa, which either did not strip completely or is also detected by the anti-PERK antibody as it is also visible on that film. White boxes indicate the image areas presented in Fig. 2 D. Visible at the bottom of the image is the lower border of the swatch and the upper edge of another membrane swatch.

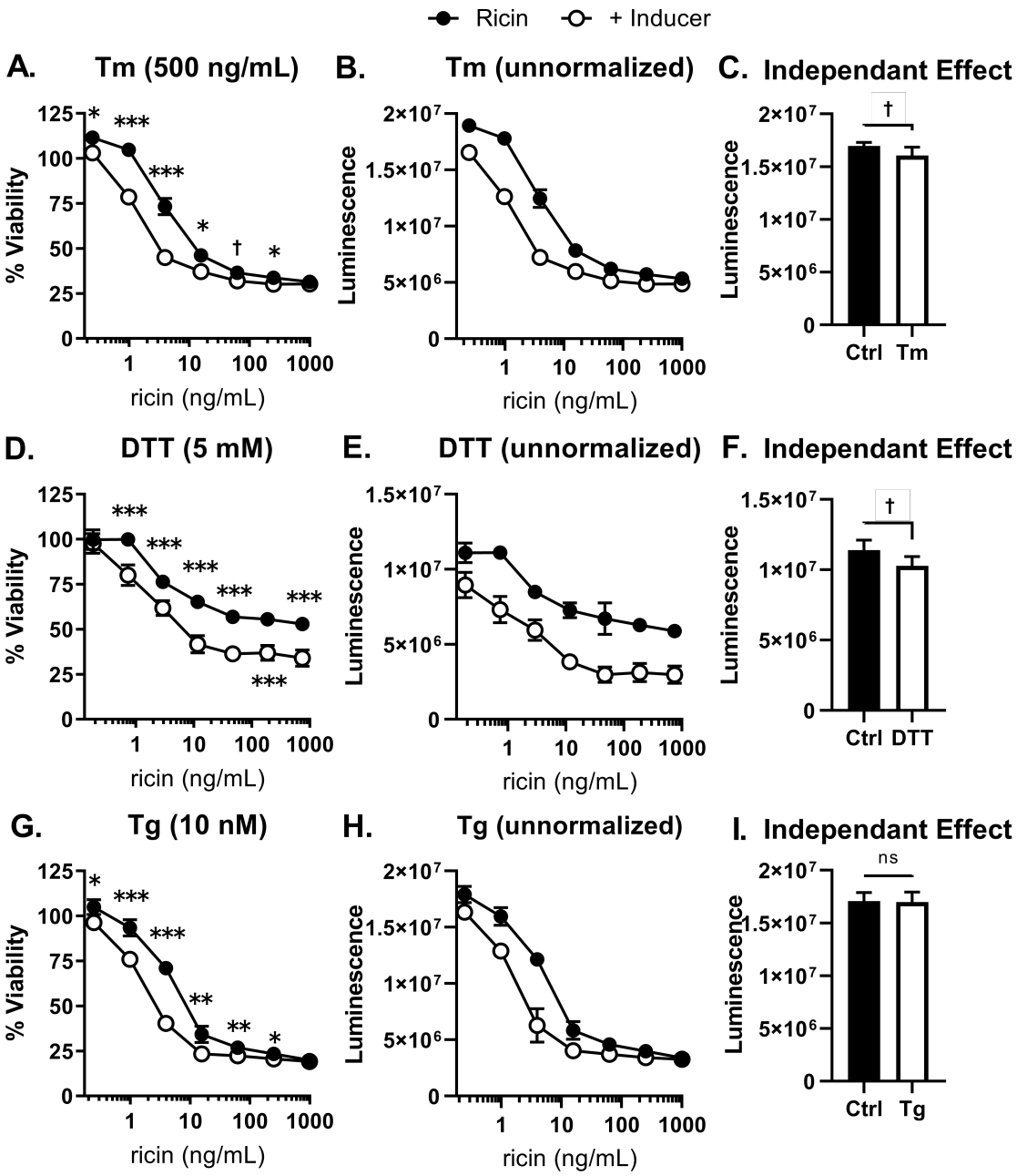
Supplemental Figure 7



Supplemental Figure 7: External induction of ER stress in dTHP-1 cells further sensitizes to ricin induced cell death

A companion to Figure 4. Treatment with tunicamycin (**A** – **C**), DTT (**D** – **F**), or thapsigargin (**G**, **H**) significantly enhanced ricin induced cell death. A statistically significant interaction between ERS inducing treatment and ricin induced lethality was observed across a range of ricin concentrations, after correcting for independent toxicity of both tunicamycin (**A**) and DTT (**D**). Plots of the raw luminescence values derived from the Cell Titer Glo viability assay are displayed in panels **B** and **E** for comparison. Bar graphs comparing raw luminescence of untreated control cells and tunicamycin (**C**) or DTT (**F**) treated cells identify the presence of statistically significant independent toxicity of these treatments. Thapsigargin exhibited a dose-dependent significant interaction with ricin induced cell death as well, without significantly effecting cell viability on its own (**G**). In the absence of confounding independent toxicity, plotting the raw luminescence visually reproduces this trend (**H**). Statistical significance of pairwise comparisons represented as follows: †, $P < .05$; *, $P < .01$; **, $P < .001$; ***, $P < .0001$

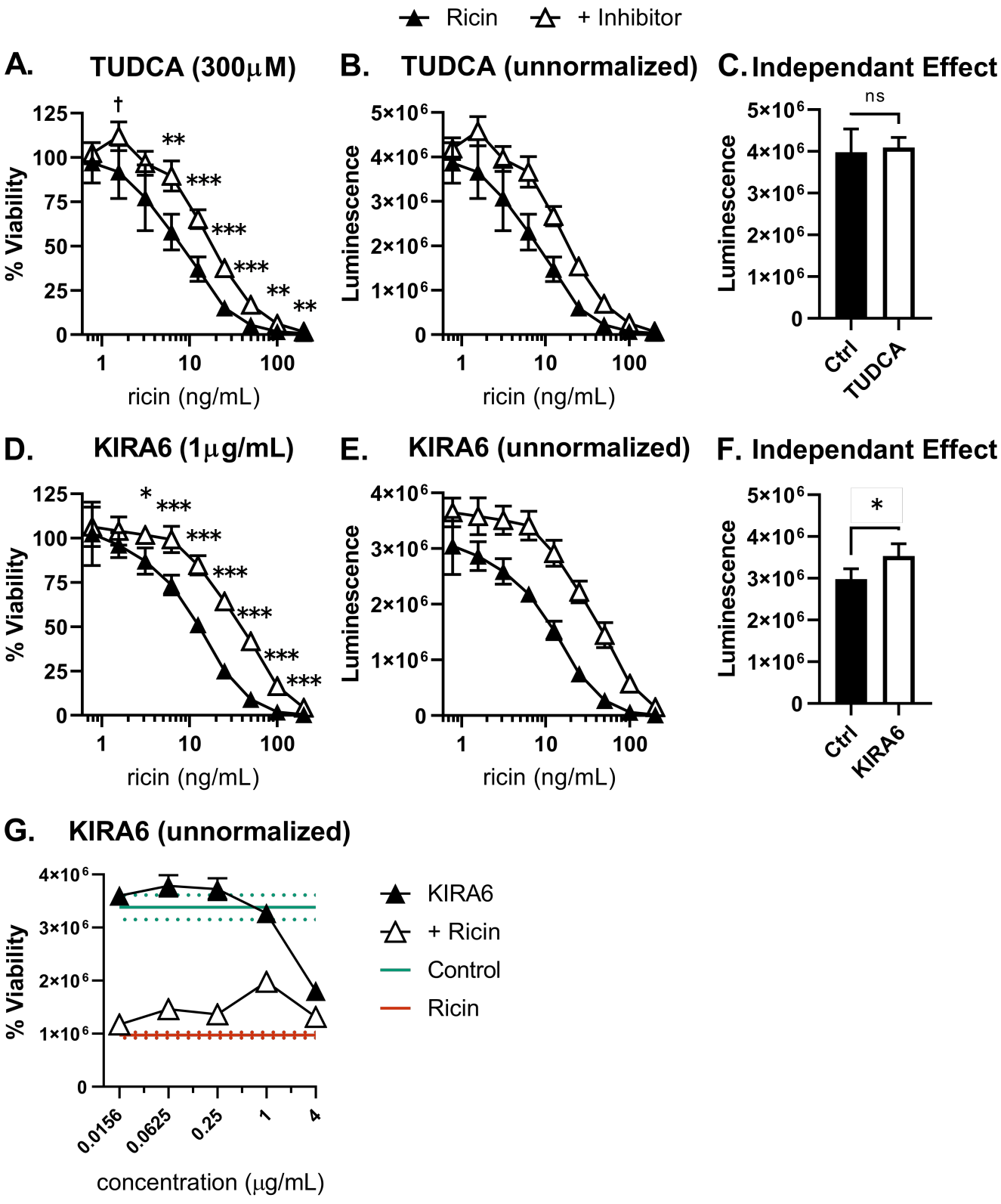
Supplemental Figure 8



Supplemental Figure 8: Treatment with ER stress inducers enhanced ricin toxicity in A549 cells

A companion to Figure 5. Treatment with tunicamycin (**A** – **C**), DTT (**D** – **F**), or thapsigargin (**G** - **I**) significantly enhanced ricin induced cell death. A statistically significant interaction between ERS inducing treatment and ricin induced lethality was observed across a range of ricin concentrations, after correcting for independent toxicity of both tunicamycin (**A**) and DTT (**D**) and without need for correction in the case of thapsigargin (**G**). Plots of the raw luminescence values derived from the Cell Titer Glo viability assay are displayed in panels **B**, **E**, and **H** for comparison. Bar graphs comparing raw luminescence of untreated control cells and tunicamycin (**C**), DTT (**F**), or thapsigargin (**I**) treated cells identify the presence of statistically significant independent toxicity of tm and DTT exposure. Statistical significance of pairwise comparisons represented as follows: †, $P < .05$; *, $P < .01$; **, $P < .001$; ***, $P < .0001$.

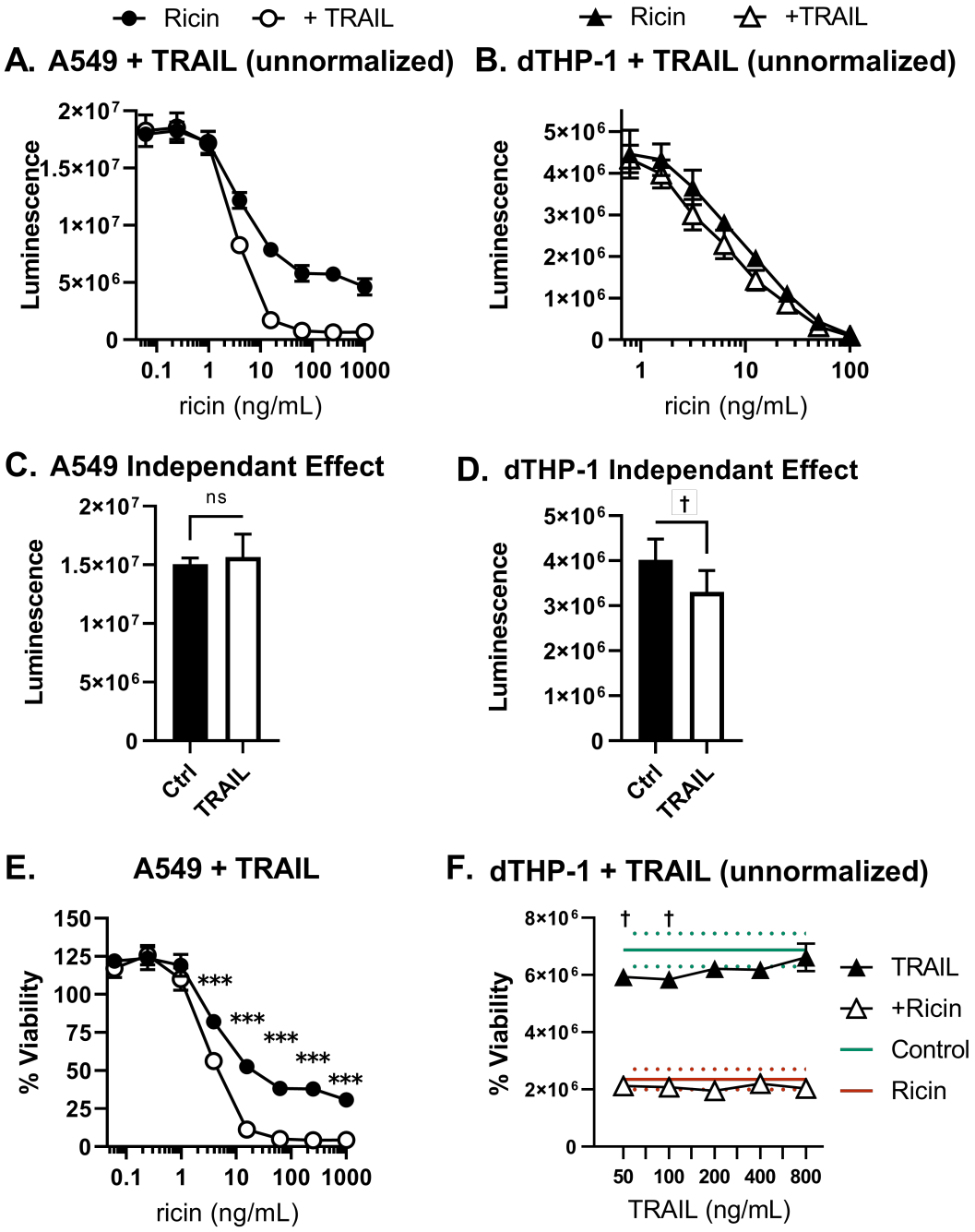
Supplemental Figure 9



Supplemental Figure 9: ER stress contributes to dTHP-1 ricin sensitivity through IRE1 activity

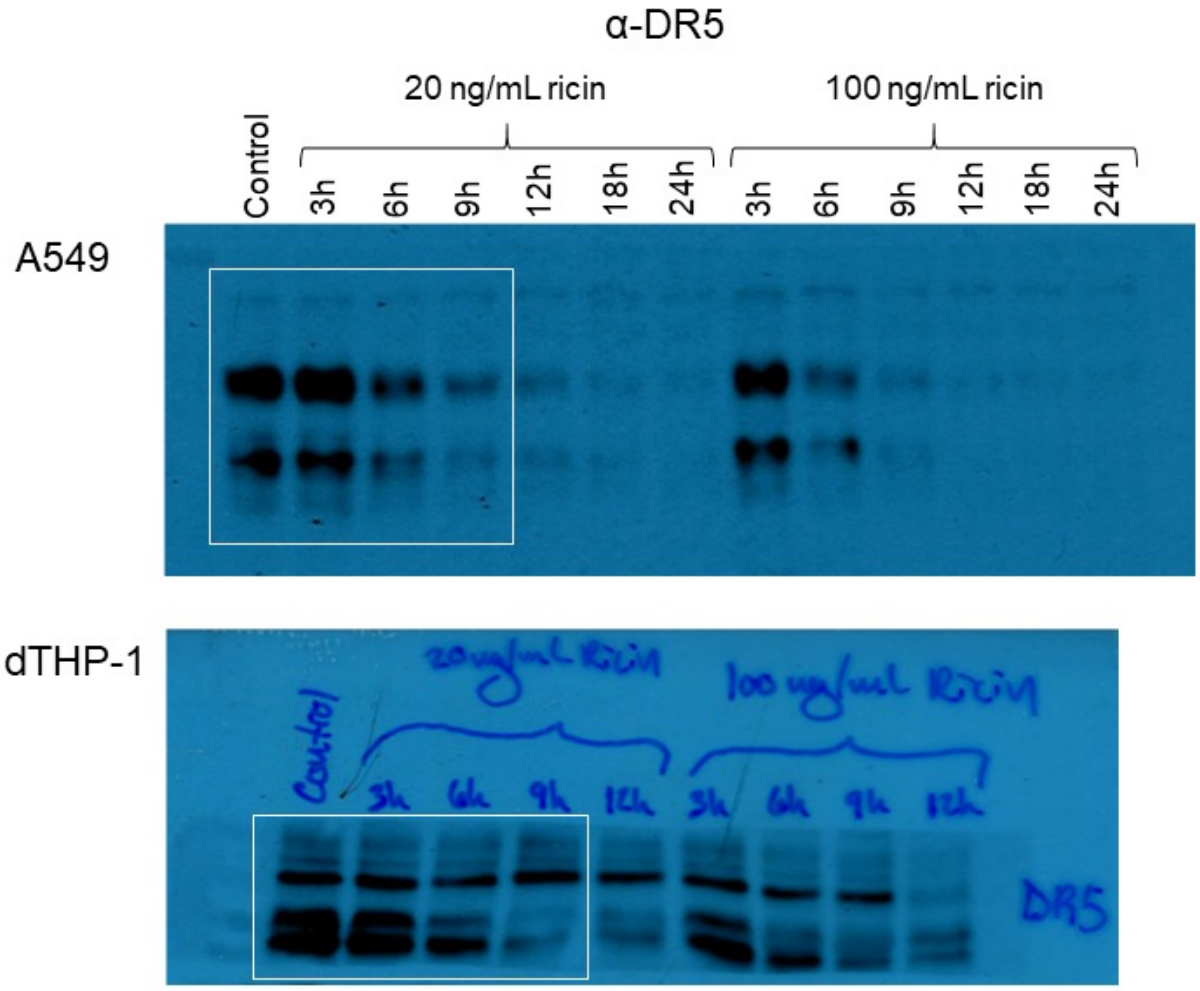
A companion to figure 6. Treatment with TUDCA (**A**) or KIRA6 (**D**) significantly rescued ricin induced cell death across a range of ricin concentrations. Plots of the raw luminescence values derived from the Cell Titer Glo viability assay are displayed in panels **B** and **E** for comparison. Bar graphs comparing raw luminescence of untreated control cells and TUDCA (**C**) or KIRA6 (**F**) treated cells show the presence of a significant independent treatment effect for KIRA6 only. KIRA6 was found to exert significant toxicity at a concentration of 4 µg/mL, which still rescued ricin induced cell death when this effect was corrected for. Panel **G** displays the raw luminescence data from this experiment, which can be compared to the normalized data presented in Figure 6 C. Statistical significance of pairwise comparisons represented as follows: †, $P < .05$; *, $P < .01$; **, $P < .001$; ***, $P < .0001$.

Supplemental Figure 10



Supplemental Figure 10: Impact of TRAIL on A549 and dTHP-1 sensitivities to ricin

A companion to Figure 7. Combinatorial treatment with ricin and TRAIL had a striking effect on A549 cell viability (**A**, **E**) but little impact on dTHP-1 (**B)** cell viability in comparison to ricin treatment alone, as shown by graphs of raw luminescence values. In A549 cells, TRAIL had no significant independent toxicity (**C**). TRAIL treatment did however produce significant independent toxicity in dTHP-1 cells (**D**), which accounted for the marginal difference in viability between ricin-only treatment and combined treatment observed in the unnormalized data. A plot of raw luminescence data finding no dose-dependent interaction between TRAIL and ricin induced cell death in dTHP-1 cells, which can be compared to the normalized data provided in Figure 7 C. Statistical significance of pairwise comparisons represented as follows: †, $P < .05$; *, $P < .01$; **, $P < .001$; ***, $P < .0001$.



Supplemental Figure 11: A549 and dTHP-1 cell DR5 blot films
Full film areas of membrane swatches probed with anti-DR5 antibody. Membrane swatches were cut just above the ~70 kDa ladder band and just below the ~35 kDa ladder band. DR5 is expected to produce two bands at 40 and 48 kDa, which is observed in A549 cells. In dTHP-1 cells, the lower molecular weight entity presents with a doublet band, also seen in some of the cell types used for demonstration in the product specification documents. White boxes indicate the film areas shown in Figure 7 D.