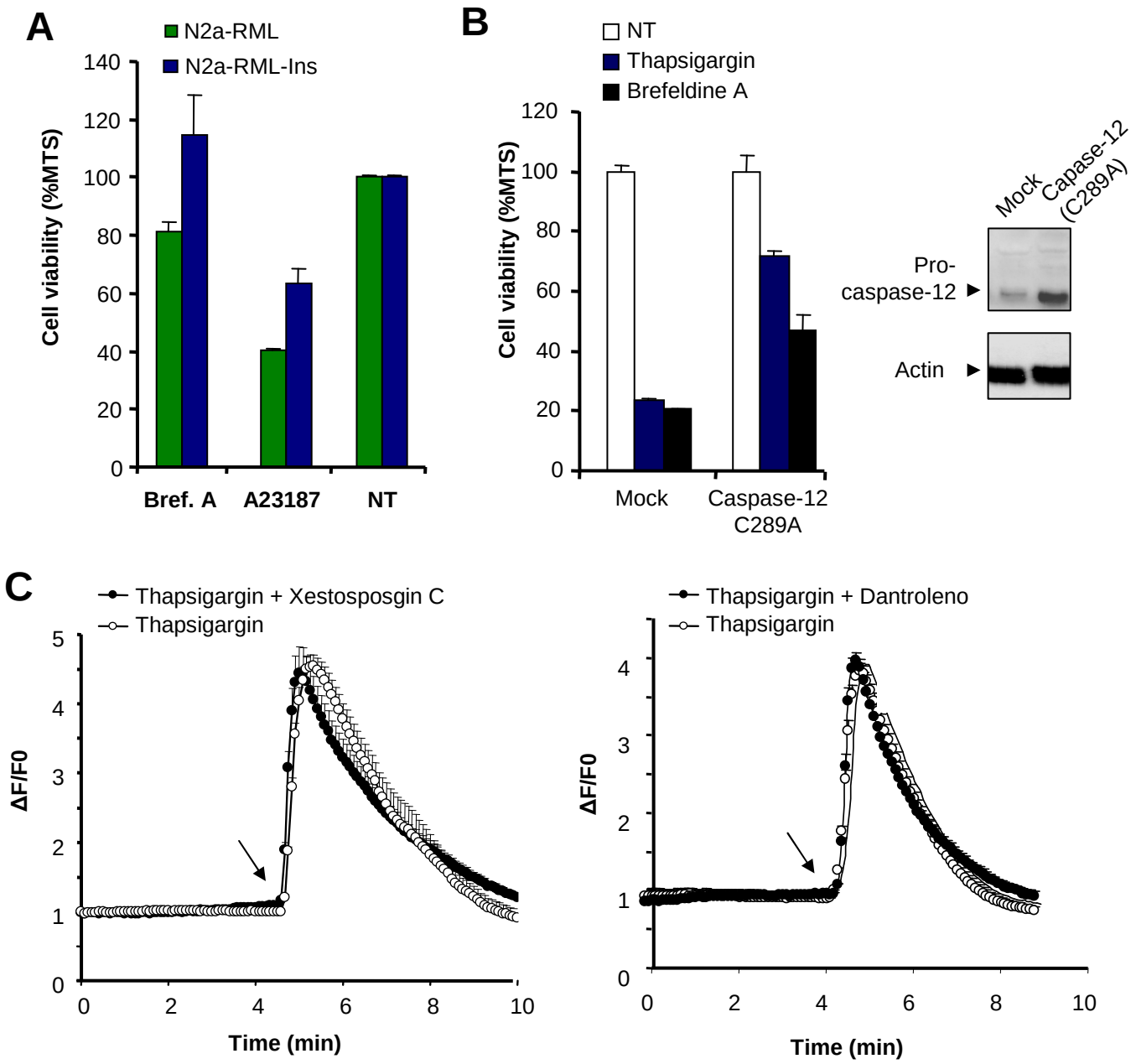

Figure S1. Control experiments. (A) ***Replication of PrP^{RES} at expenses of endogenous PrP^{C} is required to increase the susceptibility to ER stress.*** Two different Neuro2a clones were selected by their property to sustain replication of RML prions (N2a-RML) or that are resistant to replication (N2a-RML-Ins). Cell were exposed to RML scrapie prion and after several weeks in culture, they were treated with 12 µM brefeldin A (Bref. A) or 40 nM A23187. After 48h cell viability was monitored using the MTS assay. Mean and standard deviation is presented of three determinations. **(B)** ***Expression of a caspase-12 dominant negative mutant form protect against ER stress.*** Left panel: Neuro2 cells were stably transfected with empty pCDNA.3 vector or an expression vector for a caspase-12 dominant negative (C289A) construct. Then, cell viability was monitored after exposure of cells to 12 µM brefeldin A or 5 µM thapsigargin for 48h using the MTS assay. Data represent mean and standard deviation of three determinations. Right panel: Expression levels of caspase-12 and actin are presented as controls. **(C)** ***Thapsigargin treatment triggers passive related of ER calcium, not affected by inhibition of IP_3R.*** Neuro2a cells were loaded with Fluo-4 and cytosolic calcium signals were monitored in cells exposed to 10 µM thapsigargin (arrow). Cells were pretreated or not with 1 µM Xestospongine B (IP_3R inhibitor) for 1h or 50 µM dantrolen (RYR inhibitor) for 30 min. All determinations were performed in the absence of extracellular calcium. A representative experiment is presented.

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