Coku, et al., Reduced ER-mitochondria connectivity promotes neuroblastoma multidrug resistance

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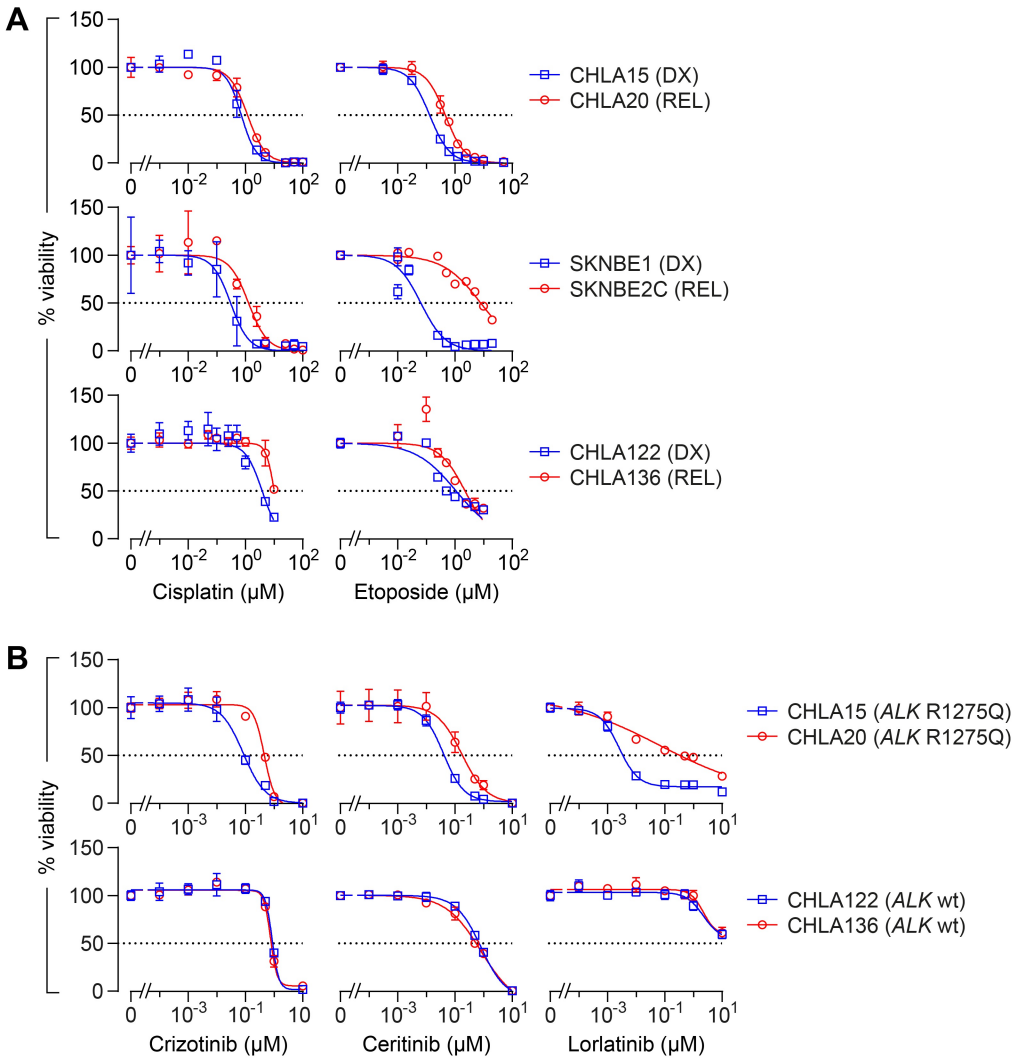
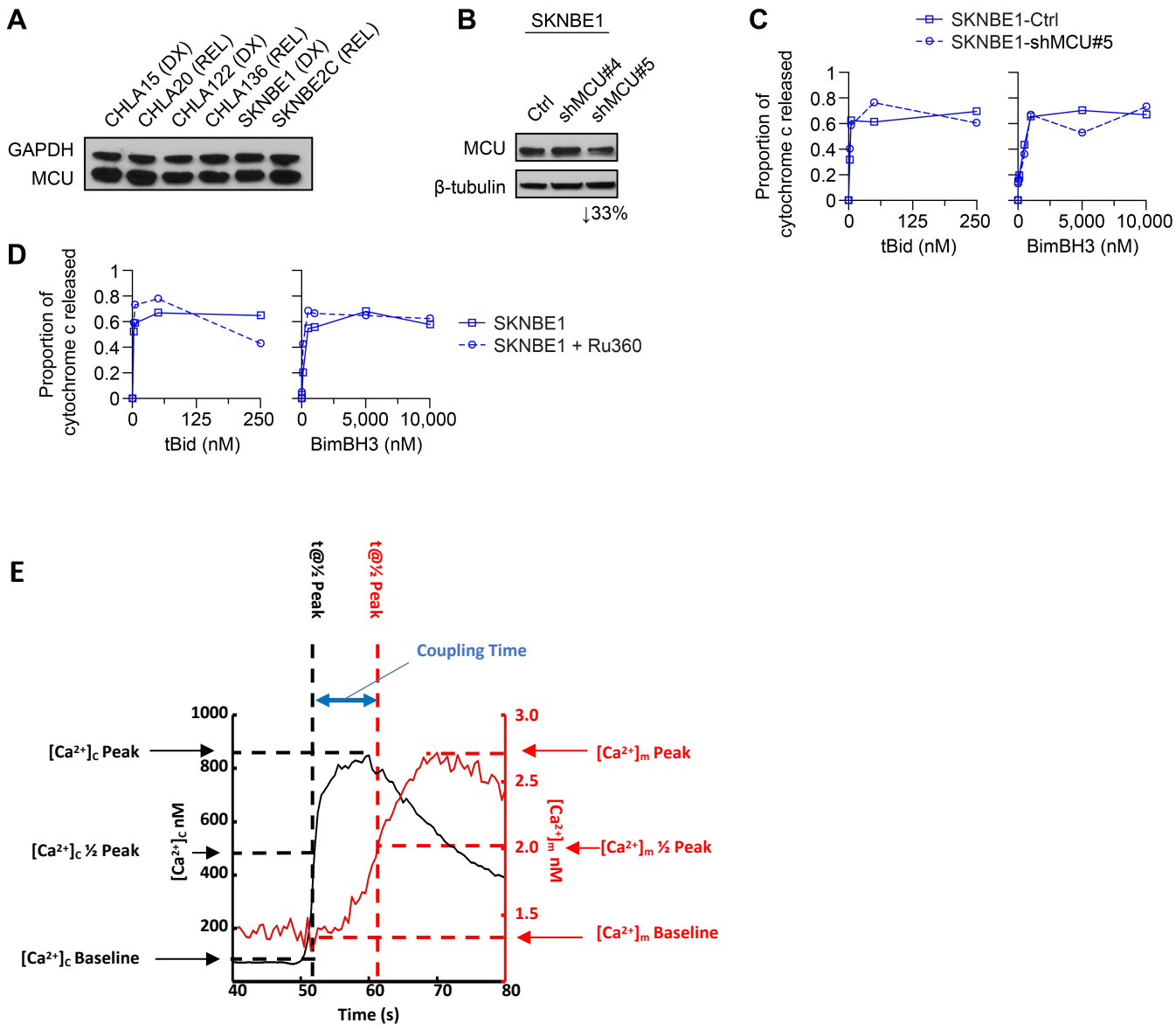


Appendix Figure S1. Most REL neuroblastomas are resistant to chemotherapeutics and molecularly targeted drugs. **(A)** In vitro viability for multiple DX/REL tumor pairs exposed to cisplatin or etoposide for 72 hours. **(B)** Viability is shown for DX/REL pairs with an activating ALK mutation (CHLA15/CHLA20) and without (CHLA122/CHLA136) following 120 hour exposure to the Alk inhibitors crizotinib, ceritinib or lorlatinib. Data points are mean and SD from triplicate wells, experiments are representative of at least three biological replicates.



Appendix Figure S2. Attenuating transfer of calcium from ER to mitochondria does not attenuate mitochondrial stress responses. (A) Immunoblot detection of MCU (mitochondrial calcium uniporter) expression across patient-matched pairs of at-diagnosis (DX) and post-relapse (REL) neuroblastomas. **(B)** Silencing of the mitochondrial calcium uniporter (MCU) in SKNBE1 cells, with ~33% reduction in MCU at the protein level in SKNBE1-shMCU#5. **(C)** Mitochondrial cytochrome c release for SKNBE1-shMCU#5 cells following exposure to tBid or BimBH3 peptide. **(D)** Mitochondrial cytochrome c release for SKNBE1 cells following exposure to tBid or BimBH3 peptide, with or without 30-minute Ruthenium-360 pre-treatment (Ru360). **(E)** Schematic representation of the coupling time metric derived from concurrent measurement of cytosolic Ca^{2+} and mitochondrial Ca^{2+}. For C and D, data points are mean of duplicate wells (SD<0.05 at all points) in a representative experiment from at least three biological replicates.