**Supplementary Experimental Procedures**

***Drug Treatment and Protein Extraction***

Panc-1 cells were seeded into replicates of 100 mm culture dishes at the density of $3.5\times10^5$ cells that were allocated into 4 groups: (a) vehicle-treated controls (n=4), (b) birinapant-treated (100 nM) (n=12), (c) paclitaxel-treated (10 nM) (n=12), and (d) birinapant/paclitaxel combined (100 nM/10 nM) (n=12). Then samples were harvested at each of the four time points: 6, 24, 48, and 72 h. Both adherent and detached viable cells were harvested and combined because cell detachment occurs early in the apoptotic response cascade(1, 2). The cell monolayers were harvested using ACCUTASE (EMD Millipore, Temecula, CA) and then washed by centrifugation (300g for 5 min) with Dulbecco's phosphate buffered saline (PBS). Detached cells were harvested from the cell culture supernatant by centrifugation. The cell pellets were combined and washed thrice in PBS and then resuspended in lysis buffer (50 mM Tris-formic acid, 150 mM NaCl, 0.5% sodium deoxycholate, 2% SDS, 2% NP-40, pH8.0) containing a cOmplete™ protease inhibitor cocktail tablet (Roche Applied Science, Indianapolis, IN) and a PhosSTOP™ phosphatase inhibitor cocktail tablet (Roche Applied Science, Indianapolis, IN) at the equivalent of $10^6$ cells per 500 μL. The lysate was incubated on ice for 30 min with vortexing every 10 min, and then homogenized 5-10 times with a Polytron homogenizer (Kinematica AG, Switzerland) for 5-10 s at 15,000 rpm with 20 s-cooling cycles. The mixture was then sonicated with a probe sonicator (3-5 cycles of 20 sec each) in order to achieve extensive lysis. The samples were centrifuged at 20,000g for 30 min at 4 °C, and then the supernatant was collected, the protein yield was measured with BCA protein assay (Pierce Biotechnology, Inc., Rockford, IL) and it was stored at -80 °C until analysis.

***Surfactant-aided-precipitation/on-pellet Digestion (SOD)***

A 50 μL aliquot containing 100 μg of extracted protein was diluted with an equal volume of 50 mM Tris-formic acid (FA) buffer (pH 8.5) L. Then 200 mM DTT was added to a final concentration of 10 mM. After incubation at 56 °C for 30 min in a Eppendorf Thermomixer (Eppendorf, Hauppauge, NY), 500 mM Iodoacetamide(IAM) solution was added to each sample to a final concentration of 20 mM. Samples were then incubated at 37 °C for 30 min in darkness with rigorous oscillation. For pellet precipitation, one volume

of chilled acetone (-20°C) was gently added into each sample and mixed for 1 min to obtain a cloudy suspension. Then another 8 volumes of chilled acetone were added to the mixture to precipitate proteins. The solution was vortexed until it became clear and stored at -20°C overnight to allow complete precipitation. Subsequently, samples were centrifuged at 20,000g for 30 min at 4 °C to obtain a protein pellet. After removing the supernatant, 500 μL chilled acetone/water mixture (85/15, v/v %) was added to wash the pellet. The tube was manipulated to enable the acetone/water mixture to cover the pellet. Samples were the centrifuged for 3-5 min, acetone/water supernatant was discarded, and the sample was allowed to air-dry.

For protein digestion, the pellet was dissolved in 100 μL Tris-FA (pH=8.5) buffer and sonicated in a water bath at 37 °C. Then 80 μL Tris-FA buffer was added to 20 μg enzyme powder (Sigma) on ice for activation. The digestion procedure composed 2 steps: 1) activated trypsin was added to the samples at a ratio of 1:40 (enzyme: substrate) and incubated for 6 h at 37 °C in a Eppendorf Thermomixer; 2) a second aliquot of trypsin solution with equal volume was added to the samples and incubated overnight. To terminate the digestion, 1% formic acid was added to each sample, gently vortexed, and then after centrifugation at 20,000g for 20 min at 4 °C, 2/3 of the digestion solution was carefully transferred into a tube for LC-MS analysis.

**References**

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