Resistance to anti-microtubule drug-induced cell death is determined by regulation of BimEL expression

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Abstract

Anti-microtubule agents are frequently used as anti-cancer therapeutics. Cell death induced by these agents is considered to be due to sustained mitotic arrest caused by the activation of spindle assembly checkpoint (SAC). However, some cell types are resistant to mitotic cell death. Cells' ability to escape mitotic arrest (mitotic slippage) is thought to be a major mechanism contributing to this resistance. Here, we show that resistance to cell death induced by anti-mitotic agents is not linked to cells' capacity to undergo mitotic slippage as generally believed but is dependent on the state of BimEL regulation during mitosis. While transcriptional repression of BimEL in the mitotic death resistant cells involves Polycomb Repressive Complex 2 (PRC2) mediated histone trimethylation, the BimEL protein is destabilized by cullin 1/4A-βTrCP dependent degradation involving activation of cullin 1/4A by neddylation. These results imply that pharmacological augmentation of BimEL activity in anti-microtubule drug resistant tumors may have important therapeutic implications.

Figure

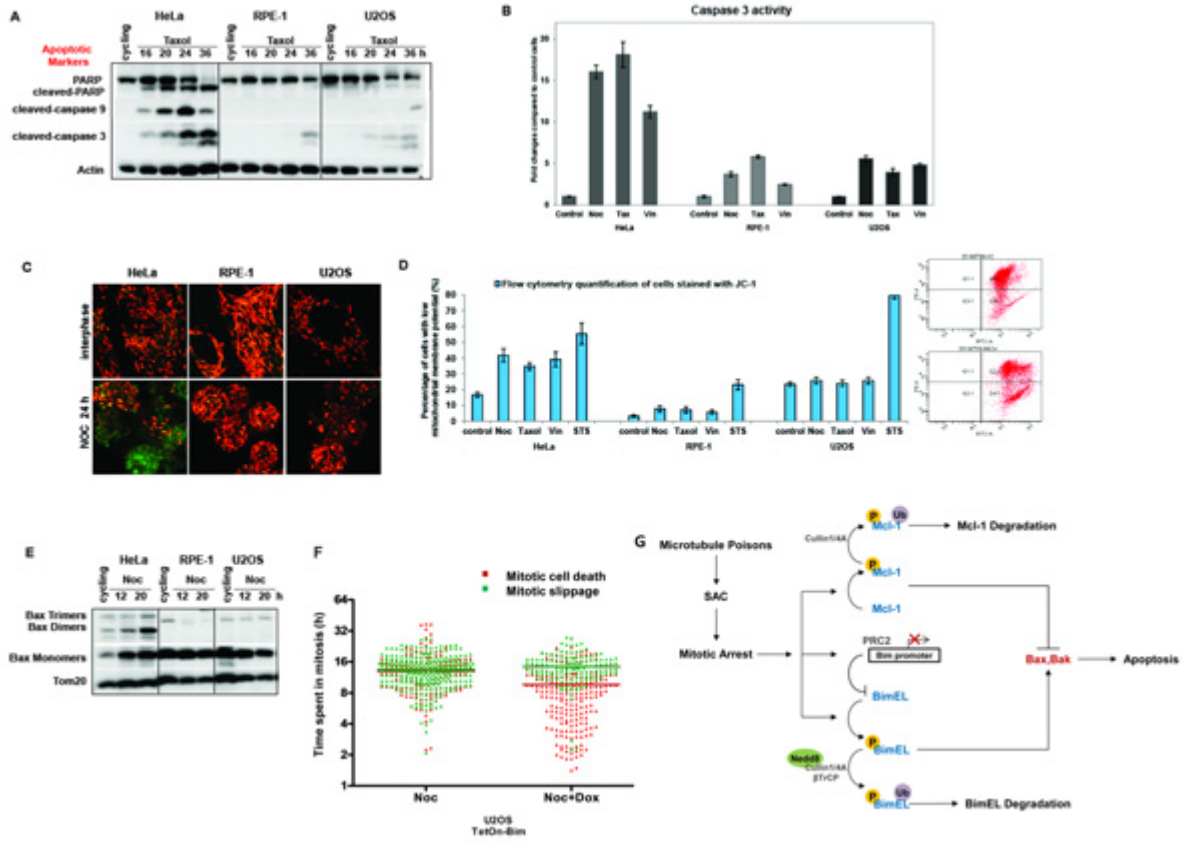

Figure Legend: A, Immunoblots of apoptotic markers in the three cell lines with Taxol treatment; **B**, Quantification of caspase 3 activity; **C**, Representative live cell imaging of changes in mitochondrial membrane potential using JC-1 staining; **D**, Left panel, quantification of cells with low mitochondrial membrane potential by flow cytometry after treatment with microtubule poisons or STS; Right panel, representative flow cytometry dot plots of untreated and nocodazole treated HeLa cells stained with JC-1; FITC-A represents emission channel of 488 nm and PE-A represents emission channel of 594 nm; **E**, Bax oligomerization in mitochondrial fraction during mitotic arrest; **F**, Quantification of mitotic time span, cell fates and mitotic death percentages by time-lapse microscopy in U2OS cells with inducible over-expression of BimEL **G**, A schematic model of the regulation of cell death in prolonged mitosis by BimEL. Noc, nocodazole; Vin, Vincristine; Tax, Taxol; STS, Staurosporine.