Depression of mitochondrial bioenergetics is a potent death stimulus in the ovarian cancer stem cells

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BACKGROUND

- Cancer stem cells represent the cell population responsible for tumor initiation and progression.
- In ovarian cancer, the CD44+/MyD88+ epithelial ovarian cancer (EOC) stem cells represent the chemoresistant population.
- We previously showed that the novel isoflavone derivative, NV-128, can induce caspase-independent cell death in the EOC stem cells.
- We demonstrate in this study that NV-128 is able to depress mitochondrial function leading to the activation of two independent cell death pathways in these chemoresistant cells.

METHODS

A panel of CD44+/MyD88+ EOC stem cells was treated with NV-128 (10μg/ml). Inhibitory studies were done using the specific MEK inhibitor, U0126 (10μM), or the ROS scavenger, MnTBAP (50μM). Mitochondrial function was assessed using the JC1 dye, MitoSox dye, and ApoSENSOR ADP/ATP kit. Protein levels were determined using Western Blot.

KEY FINDINGS

1. NV-128 is able to elevate mitochondrial superoxide levels and inhibit ATP production in the EOC stem cells.
2. Superoxide production activates the ERK/Bax axis, which results in loss of mitochondrial membrane potential.
3. Loss of ATP activates AMPKα1, leading to mTOR inhibition.
4. Depression of mitochondrial function is associated with loss of Cox-IV.

CONCLUSION

- Depression of mitochondrial function is a potent stimulus to induce cell death in the EOC stem cells and opens new venues for treating ovarian cancer patients.
- Novel NV-128 derivatives such as NV-344, are being developed with improved potency.