

US EPA ARCHIVE DOCUMENT

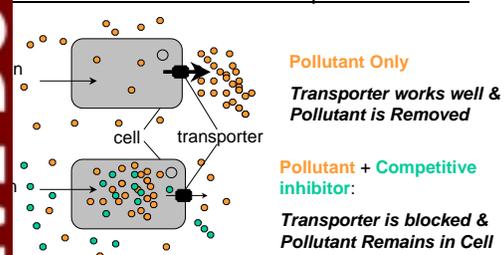


US EPA ARCHIVE DOCUMENT

Enhanced Sensitivity to Toxicants via Inhibition of ABC Transporters

Abstract
 This study demonstrates that increased sensitivity to toxicants or “chemo-sensitization” via inhibition of multi-drug transporters leads to cellular disruption, apoptosis, and embryo mortality.

Chemo-sensitization via Transporter Inhibition



Our Question:

Does inhibition of efflux transporters lead to secondary toxicity, apoptosis, and embryo mortality?

Our Model: The purple sea urchin embryo



Our Approach:

Monitor apoptosis and survival of urchin embryos.

Determine if the addition of known inhibitors of efflux transporters increases apoptosis and decreases embryo survival.

Apoptosis Across Normal Development

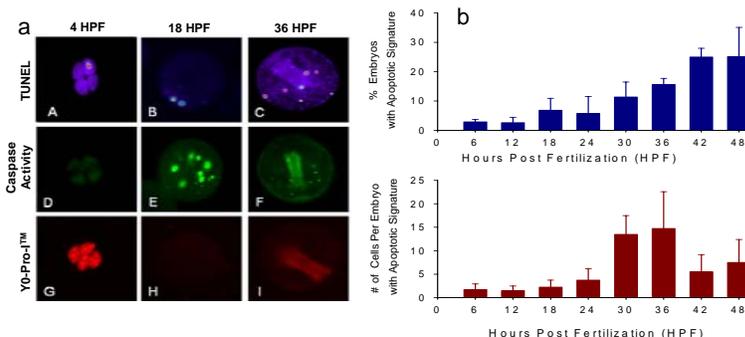


Figure 1. Using 3 assays we found that urchin embryos delete cells only around the hatching stage, never before, and rarely afterwards (a). Apoptosis is infrequent throughout normal urchin development. The number of cells dying in each embryo peaks around the gastrula stage (b).

Chemically Induced Apoptosis Across Development

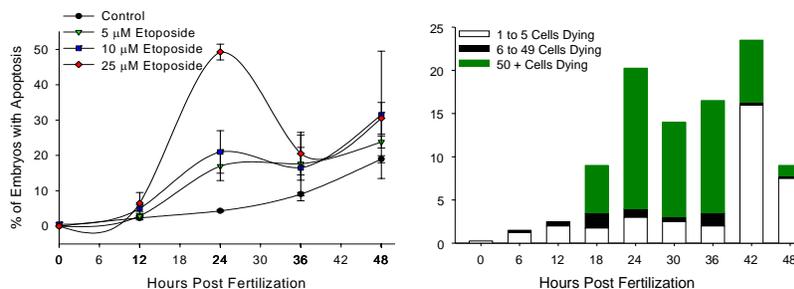


Figure 2. Exposure to genotoxic chemicals does not induce apoptosis during cleavage. Chemical induced apoptosis peaks around the stage hatching. Urchin embryos are surprisingly resistant to apoptosis (<50% of embryos) even in the presence of high concentrations of genotoxic chemicals (Vega and Epel, 2004).

Apoptosis Increases After Transporter Inhibition

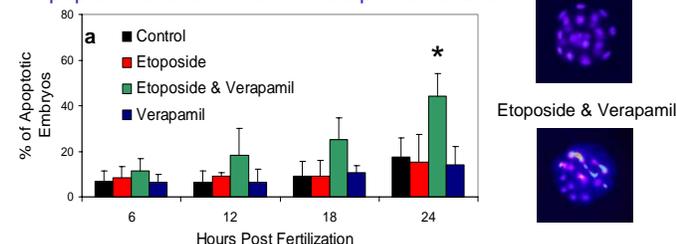


Figure 3. Apoptosis (a) and embryo DNA quality (b) is only affected when both etoposide (1μM) and the transport inhibitor, verapamil (.75μM) are combined (in press, Mutation Research).

Chemo-sensitization via Inhibition of ABC Transporters

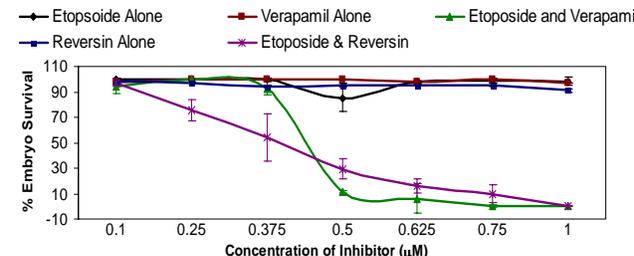


Figure 4. We found a marked reduction in survival after exposure to both the genotoxin etoposide (5μM) and increasing concentrations of the transporter inhibitors, verapamil and reversin 205. Etoposide and the inhibitors have no affect separately.

Conclusions

- * Disruption of multi-drug transporters in the presence of seemingly benign concentrations of genotoxins can lead to increased apoptosis and embryo mortality.
- * This study provides evidence for the hypothesis that chemo-sensitization has real life consequences to aquatic embryos.