Abstract

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Project Title : Interrogation of natural products using a *Saccharomyces cerevisiae* chemical genetic synthetic lethality screen to identify anticancer agents

Investigator : Assoc. Prof. Laran T. Jensen

Faculty of Science, Mahidol University

E-mail Address : laran.jen@mahidol.ac.th

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Reduced activity of *ERCC4* has been documented in more than 50% of colorectal cancer cases examined, making this gene an interesting target for the identification of compounds with chemical synthetic lethal properties. We utilized the baker's yeast *S. cerevisiae* to search for plant material that displayed synthetic lethal interactions with yeast deleted for *RAD1*, the homologue of human *ERCC4*. *Bacopa monnieri* was identified as having synthetic lethal effects in the *rad1*Δ cells. Yeast lacking the Rad1p interacting protein Rad14p, involved in nucleotide excision repair pathway, did not display similar sensitivity to *B. monneiri* extracts as *rad1*Δ cells, suggesting that loss of the double-strand break repair function of Rad1p likely contributes to enhanced sensitivity to *B. monneiri* extracts. Exposure to *B. monneiri* extracts resulted in nuclear fragmentation and elevated levels of ethidium bromide staining in *rad1*Δ yeast suggesting promotion of an apoptosis-like event. Analysis of known constituents from *B. monneiri* identified a chemical genetic interaction between bacopasaponin C and *rad1*Δ yeast. Bacopasaponin C may be a drug candidate or serve as a model for the development of analogs for the treatment of colorectal cancer. Our analysis also noted several plant extracts that exhibited potential antifungal properties. The antifungal activity of *Aglaia odorata, Colubrina asiatica, Bacopa monnieri, Melodorum fruticosum* appears to be mediated at least in part through induction of proteotoxic stress and damage to the vacuole and mitochondria.