Reviewer’s report

Title: The induction of activating transcription factor 3 (ATF3) contributes to anti-cancer activity of Abeliophyllum distichum Nakai in human colorectal cancer cells

Version: 2 Date: 26 August 2014

Reviewer: Gayathri Chadalapaka

Reviewer’s report:

The manuscript ‘The induction of activating transcription factor 3 (ATF3) contributes to anticancer activity of Abeliophyllum distichum Nakai in human colorectal cancer cells’ by Jin Boo Jeong et al. reports the following key findings:

• The anti-cancer activity of EAFAD-B may be a result of ATF3 promoter activation and subsequent increase of ATF3 expression.

• EAFAD-B acts as an anticancer agent in human colorectal cancer cells, breast cancer cells and hepatocellular carcinoma and caused a significant reduced the cell viability.

• EAFAD-B increased the expression of activating transcription factor 3 (ATF3) and promoter activity via transcriptional activation. Also authors report that EAFAD-B contributes at least in part to increase of ATF3 accumulation.

• Suggested EAFAD-B-responsible sites on the ATF3 promoter are between -147 and -85 region of the ATF3 promoter.

• EAFAD-B-induced ATF3 promoter activity was significantly decreased when the CREB site was deleted, indicating CREB mediated ATF3 modulation.

• Inhibition of p38MAPK and GSK3β attenuated EAFAD-B mediated ATF3 promoter activation.

Very few reports are available on Abeliophyllum distichum Nakai extracts. One of the reports suggests that it has antioxidative activity and inhibits DNA damage. Another report by one of the authors suggests anticancer activity of the same extract is via proteosomal degradation of Cyclin D1 by threonine-286 phosphorylation.

The manuscript is well written, experiments are well designed and the work is well presented. The data clearly supports the hypothesis and has implications in understanding anticancer activity of EAFAD-B via ATF3 promoter activation and subsequent increase of ATF3 expression.

Minor Essential Revisions

Here are some comments to improve the quality of this report:
1. Is the dose used in this study bio-relevant? What is the rationale for choosing this dose? Because the authors use colorectal cancers, its clinical relevance would be significant if the availability of the drug at the cancer specific site would be justifiable.

2. Plant derived agents always carry a risk of toxicity and off target effects. Did the authors evaluate the toxicity of this drug? This has to be evaluated using normal or immortalized cells specific to the organ of cancers.

3. The authors use colon, breast and HepG2 in the screenings but only use colon cancer cells in rest of the experiments. Were similar results seen with other cancer types also?

4. The data is very well conducted and presented. Did the authors perform any xenograft studies? Or was this report meant to be a pilot study? It would be interesting, at least in future, to see how this drug performs in animal models.

5. "In time-course experiment, ATF3 promoter activity was increased at 3 h after EAFAD-B treatment in both HCT116 and SW480 cells (Fig. 2G and H), while, ATF3 protein expression was slightly induced at 1 h after EAFAD-B treatment" Usually, mRNA or promoter activity induction occurs prior to the protein. But it appears to be the reverse here. Is there an explanation for this?

Discretionary Revisions

Here are few comments 'not' related to the scientific content of the manuscript. Interestingly, Abeliophyllum distichum Nakai is close to extinction and qualifies for the IUCN Category of 'Critically Endangered', indicating a high risk of extinction in the near future. For future clinical trials and mass drug testing, this plant extracts would be needed in abundance. But based on the extinction status, the practical application of this drug as an anticancer agent in patients might be questionable.

Secondly it is limited extremely to a limited geographic distribution which is South Korea. It is difficult to see a worldwide applicability of this agent as a drug in future, added to its endangered status.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests.