Title: Inhibition of STAT3 signaling and induction of SHP1 mediate antiangiogenic and antitumor activities of ergosterol peroxide in U266 multiple myeloma cells

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Author's response to reviews: see over
Dear Dr. Jigisha Patel MRCP, PhD, Editor-in-Chief:

Enclosed was a manuscript by Yun-Hee Rhee, Soo-Jin Jeong, Hyo-Jeong Lee, Hyo-Jung Lee, and Sung-Hoon Kim, entitled “Inhibition of JAK2/STAT3 signaling and induction of SHP1 mediate antiangiogenic and antitumor activities of ergosterol peroxide in U266 multiple myeloma cells” which we would like to be considered for publication in BMC Cancer.

Ergosterol peroxide (EP) derived from edible mushroom has been shown to exert anti-tumor activity in several cancer cells. In the present study, anti-angiogenic activity of EP was investigated with the underlying molecular mechanisms in human multiple myeloma U266 cells.

Despite weak cytotoxicity against U266 cells, EP suppressed phosphorylation, DNA binding activity and nuclear translocalization of signal transducer and activator of transcription 3 (STAT3) in U266 cells at nontoxic concentrations. Also, EP inhibited phosphorylation of the upstream kinases Janus kinase 2 (JAK2) and Src in a time-dependent manner. Furthermore, EP increased the expression of protein tyrosine phosphatase SHP-1 at protein and mRNA levels, and conversely silencing of the SHP-1 gene clearly blocked EP-mediated STAT3 inactivation.

In addition, EP significantly decreased vascular endothelial growth factor (VEGF), one of STAT3 target genes at cellular and protein levels as well as disrupted in vitro tube formation assay.

Moreover, EP significantly suppressed the growth of U266 cells inoculated in female BALB/c athymic nude mice and immunohistochemistry revealed that EP effectively reduced the expression of STAT3 and CD34 in tumor sections compared to untreated control.

Overall, these findings suggest that EP can exert antitumor activity in multiple myeloma U266 cells partly with antiangiogenic activity targeting JAK2/STAT3 signaling pathway as a potent cancer preventative agent for treatment of multiple myeloma cells.

We would like to suggest the following individuals as potential reviewers of our study; Prof. Chang-Yan Chen (Harvard Medical School, USA), Prof. Hongbo Hu (China Agricultural University, China) and Prof. Jake Chen (Tufts School of Medicine, USA).
We certify that these data have not been published in any primary scientific journals until now. We thank you in advance for your assistance.

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