Investigation of novel therapeutic strategies
for epithelial ovarian cancer

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Abstract

Objective: PRIMA-1MET is a small molecule compound that restores wild-type p53 to mutant p53, and is recently confirmed to be safe at therapeutic plasma levels. The aims of this study were to identify the anti-tumour activity of PRIMA-1MET on epithelial ovarian cancer (EOC) cells and elucidate the underlying mechanism in vitro.

Methods: We used nine EOC cell lines and their chronic cisplatin/paclitaxel-resistant cells and performed cell viability assay and cell apoptosis assay to evaluate the efficacy of PRIMA-1MET. Moreover, we assessed the functional role of reactive oxygen species (ROS) and their scavenger in the EOC cells.

Results: We examined the viability of the total 13 EOC cells after 48 h treatment with PRIMA-1MET. Measuring the half maximal inhibitory concentration (IC$_{50}$) of EOC cells revealed that the sensitivity was heterogeneous, and did not correlate with TP53 status. PRIMA-1MET induced apoptosis, PARP cleavage, and intracellular ROS accumulation in a p53-independent manner. The anti-tumour effects of PRIMA-1MET were completely rescued by a ROS scavenger, N-acetyl cysteine. Furthermore, PRIMA-1MET reduced the expression of antioxidant enzymes, PRX3 and GPX1, in a dose-dependent manner.

Conclusion: We demonstrated that PRIMA-1MET had an anti-tumour effect on EOC cells regardless of TP53 status and chemo-resistance. PRIMA-1MET is a promising therapeutic agent for chemo-resistant EOC patients and may contribute to a better prognosis in the future.
Declaration

I certify that this thesis contains no material which has been accepted for the award of any other degree or diploma in my name in any university or other tertiary institution except Nagoya University. To the best of my knowledge and belief, it contains no material that has previously been published by any other person except where due reference is made. In addition, I certify that no part of this work will, in the future, be used in a submission in my name for any other degree or diploma in any other university of other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint award of this degree.

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Nobuhisa Yoshikawa

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Abbreviations

µg microgram
µL microLitre
µM microMolar
bp base pairs
cDNA complimentaly DNA
DMEM Dubecco's Modified Eagle Medium
DMSO Dimethyl sulfoxide
DNA Deoxyribonucleic acid
dNTP Dinucleotide triphosphate
DSB double strand brake
ECM extracellular matrix
EMT Epithelial-to-mesenchymal transition
EOC epithelial ovarian cancer
FACS Fluorescence activated cell sorting
FBS fetal bovine serum
GFP Green Fluorescent Protein
gRNA guide RNA
HDR homology directed repair
HGSOC high-grade serous ovarian cancer
HPMCs Human peritoneal mesothelial cells
IGF Insuline like Growth Factor
M Molar
mg  milligram
mL  millilitre
MQ  methylene quinuclidinone
mRNA messenger ribonucleic acid
NaCl sodium chloride
NHEJ non-homologous end joining
PARP Poly ADP-ribose Polymerase
RPMI Roswell Park Memorial Institute medium
RT-PCR Reverse transcription real time polymerase chain reaction
shRNA short hairpin RNA
TGF Transforming Growth Factor
VEGF Vascular Endothelial Growth Factor
Conference Presentations

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