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OVARIAN DAMAGE BY ANTICANCER THERAPY: MOLECULAR MECHANISMS AND PREVENTIVE STRATEGIES

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Context: Novel management strategies have led to increased rates of cancer survivors throughout the past three decades highlighting the need for post-treatment care to improve the patient's quality of life. A serious long-term side effect of cancer therapies is the increased infertility risk due to accelerated reproductive aging leading to premature ovarian failure. A potential mechanism behind ovarian toxicity by anticancer drugs is oxidative stress (OS). An important sensor of OS is SIRT1, one of the seven members of the mammalian sirtuin family, NAD+-dependent enzymes with deacetylase activity, which orchestrates cellular defence and repair mechanisms and controls cell fate.
Objective: The aim of the study was to investigate whether the natural carotenoid Crocetin (8,8'-diapocarotenoic acid) and the synthetic tellurium compound AS101 protect the ovary against cyclophosphamide (CPM) by modulating SIRT1 and mitochondrial markers.
Methods: Female mice received vehicle, CPM, Crocetin plus CPM or AS101 plus CPM. Ovarian SIRT1 and the mitochondrial markers SIRT3, superoxide dismutase 2 (SOD2), and peroxisome proliferator receptor gamma coactivator 1 alpha (PGC1alpha) were assessed at 24 h post CPM and follicle populations were evaluated at 7 day post CPM.
Results: In CPM-mice ovaries, SIRT1 protein was found to increase revealing the occurrence of an adaptive response to OS. The mitochondrial sirtuin SIRT3 was increased, whilst SOD2 and the mitochondrial biogenesis activator PGC1alpha were reduced by CPM, suggesting that CPM-induced OS was associated with mitochondrial damage. Crocetin and AS101 administration under conditions preventing follicle damage allowed the maintenance of basal levels of SIRT1 suggesting that preservation of redox balance can help the ovary counteracting ovarian damage by CPM. We also found that SIRT3 was decreased and SOD2 and PGC1alpha were increased in mice receiving Crocetin or AS101 prior to CPM, thus providing evidence for mitochondrial protection.
Conclusions: Results from this study aims to increase the knowledge of mechanisms underlying ovarian damage by CPM and will be helpful to develop new therapeutic opportunities for preserving fertility in cancer patients based on administration of antioxidants with anticancer properties. Also, our data suggest that SIRT1 may be a biomolecular marker for evaluating the cytotoxicity of chemotherapeutic agents other than CPM and the potential of protective molecules.

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