論 文 審 査 の 結 果 の 要 旨

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（論文審査の結果の要旨）

SIRT1 is known as a longevity gene that forestalls aging and age-related diseases including cancer. However, SIRT1 has recently attracted widespread attention due to its overexpression in some cancers. We previously identified the overexpression of SIRT1 in ovarian carcinoma (OvCa) as a poor prognostic factor. Therefore, we investigated the function of SIRT1 in OvCa cells.

The cDNA, siRNA/shRNA technologies and a SIRT1 inhibitor (EX527) were utilized for the overexpression (OEX), knock-down (KD) and inhibition of SIRT1, respectively, in human OvCa cell lines. The effect of SIRT1 on proliferation and chemoresistance was examined using a WST-1 assay. To clarify the underlying mechanisms, apoptosis (Annexin V/PI staining), tumor formation ability (soft-agar colony formation assay), the expression of antioxidants and stem cell marker including CD44v (real-time PCR and western blotting), and migration and invasion ability were examined, and glutathione (GSH) and reactive oxygen species (ROS) were quantified. Accordingly, the present study has revealed the function of SIRT1 in OvCa cells as follows:

1. SIRT1 significantly enhanced the proliferation ($P<0.05$) and chemoresistance ($P<0.05$), and reduced apoptosis ($P<0.05$).
2. SIRT1-OEX significantly enhanced the colony formation ability in soft-agar and upregulated several stemness-associated genes, suggesting that SIRT1 might be involved in the maintenance of cancer cell “stemness”.
3. SIRT1 reduced oxidative stress via upregulating multiple antioxidant pathways including antioxidative enzymes, GSH, and CD44v-xCT pathways.
4. SIRT1 enhanced the migration and invasion ability of OvCa cells.

In conclusion, our results suggest that SIRT1 plays a role in the acquisition of aggressiveness and chemoresistance of OvCa, and has a potential as a therapeutic target for OvCa.

以上の論文審査の結果、主査、副査は一致して本論文を学位論文として価値があるものと認めた。