SIRT1 IS INVOLVED IN CISPLATIN RESISTANCE BY MAINTAINING GLUCOSE HOMEOSTASIS AND MITOCHONDRIAL STABILITY IN CANCER CELLS

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Tumors frequently develop resistance to cisplatin, a platinum drug used as a cornerstone of present day chemotherapy regimens, significantly decreasing its usefulness in the clinic. Although it has been shown that cisplatin-resistant (CP-r) cancer cells commonly grow more slowly, the actual mechanism of tumor resistance to cisplatin is unclear. We found reduced uptake of 2- deoxyglucose due to a mislocalized glucose transporter in CP-r cells. The CP-r cells overexpressed SIRT1 and exhibited reduced oxygen consumption and altered function and morphology of mitochondria. Incubation of drug-sensitive cells in low glucose medium induced the over-expression of SIRT1 and increased cellular resistance to cisplatin. CP-r cells with higher NAD^+ showed reduced expression of GAPDH with increasing expression of SIRT1. Expression of SIRT1 was downregulated in CP-r cells when transfected with GAPDH, which caused the CP-r cells to become sensitive to cisplatin. SIRT1 overexpression by SIRT1 cDNA transfection increased the tumor resistance to cisplatin. Overexpression of SIRT1 might restrict glucose homeostasis in cells by decreasing oxygen consumption, thereby protecting tumors from cisplatin toxicity. Our findings therefore suggest that reduced bioenergenesis mediated by SIRT1 contributes to cellular resistance to cisplatin.