Leptin receptor antagonist as a potent histone deacetylases (HDACs) inhibitor in ovarian cancer cells

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Post-translational histone modifications can play an important role in the cancer development. Leptin, produced by adipose tissue has been identified as a growth factor in certain hormone related cancers including ovarian cancer. Currently, several groups of scientists are working on synthesizing leptin receptor blockers, and number of leptin receptor antagonist were tested in breast, colon and prostate cancer, suggesting their future use in anticancer therapy. The question arises whether the leptin receptor blockers may also act as inhibitors of HDAC in ovarian cancer. As a model we used the epithelial ovarian cancer (chemoresistant-OVCAR-3 and primary-CaOV-3) and folliculoma (adult –KGN and juvenile- COV434) cell lines. Two antagonists: superactive human leptin antagonist-SHLA and quadruple leptin mutein -LAN 2 (L39A/D40A/F41A/I42A have been applied. Particular cell lines were treated with leptin in a dose of 40 ng/ml (noted in obese women) and antagonist in a dose 1000 ng/mL. Effect of blockers on HDACs (1,2,3,4,5,6 7,8,9) gene (real time PCR) and protein expression (western blot) were tested, HDACs expression was higher in OVCAR-3>CaOV-3, and higher in COV434>KGN. Leptin increased HDAC 1, 7 and 9 gene expression only in OVCAR-3, while in granulosa tumour cells increased HDAC 2, 6, 7 in KGN and 9 in COV434. SHLA was the most potent HDACs inhibitor in OVCAR-3 cells and reversed stimulatory effect of leptin on HDAC1, 9 gene, and HDAC4, 5 protein expressions. In granulosa tumor cells, Lan-2 seemed to be most potent inhibitor. Reversed stimulatory effect of leptin on HDAC9 gene expression and HDAC 1, 5 protein expression in COV434 cells in KGN cell line both antagonist reversed stimulatory effect of leptin on HDAC 5, 6, 7. It was concluded that leptin receptor antagonist as HDACs inhibitors should be emerged as an exciting new class of potential anticancer agents. However, histopathological type of cancer should be taken into consideration in the choice of leptin receptor inhibitors.

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Biography

Ewa L Gregoraszczuk specializes in Reproductive Endocrinology as well as Hormone Dependent Cancer. She graduated from the Jagiellonian University in Krakow, Poland. From 1998, she has been the Professor of Endocrinology, Head of Department of Physiology and Toxicology of Reproduction. She has authored 173 peer-reviewed articles in leading journals such as Biology of Reproduction, Reproduction, Reproductive Toxicology, Toxicology, Cancer Chemotherapy and Pharmacology. She is a Member of the Polish Endocrinology Society, International Society of Endocrinology (ISE), The New York Academy of Sciences, and The European Tissue Culture Society. She has been a Promoter for 60 MD, 16 PhD and 3 Habilitations. Her research topics are focused on the effects of metabolic hormones produced by adipose tissue in light of the increasing incidence of obesity and related problems in reproduction and hormone dependent cancer; reprotox and canceriogenic action of endocrine disruptors, testing antiepileptic drugs as a potent anticancer in combination with chemotherapy; testing leptin receptor blockers as a novel treatment for ovarian cancer.

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