

Scientific Paper:

Cancer Chemother Pharmacol, DOI 10.1007/s00280-010-1294-0

## **Pioglitazone modulates tumor cell metabolism and proliferation in multicellular tumor spheroids**

Eva Gottfried<sup>1</sup>, Sebastian Rogenhofer<sup>2</sup>, Heidi Waibel<sup>3</sup>, Leoni A. Kunz-Schughart<sup>4</sup>, Albrecht Reichle<sup>3</sup>, Monika Wehrstein<sup>3</sup>, Alice Peuker<sup>3</sup>, Katrin Peter<sup>3</sup>, Gabi Hartmannsgruber<sup>3</sup>, Reinhard Andreesen<sup>3</sup>, Marina Kreutz<sup>3</sup>

<sup>1</sup>Department of Hematology and Internal Oncology, University Medical School, Franz-Josef-Strauss-Allee 11, 93053 Regensburg

<sup>2</sup>Department of Urology, University Medical School, Bonn, Germany

<sup>3</sup>Department of Hematology and Internal Oncology, University Medical School, Regensburg, Germany

<sup>4</sup>OncoRay – Center for Radiation Research in Oncology, Dresden University of Technology, Dresden, Germany

### **Abstract:**

The anti-diabetic thiazolidinedione compound pioglitazone, a peroxisome proliferator-activated receptor-gamma agonist, and selective cyclooxygenase-2 inhibitors are clinically used in patients with advanced malignancies. Several previously published in vivo and in vitro studies showed growth inhibitory effects on different cancer cell lines. However, the underlying mechanisms are fairly unclear. Here, we analyzed the effects of pioglitazone in combination with other drugs in a three-dimensional multicellular tumor spheroid culture system (MCTS) generated from the two prostate carcinoma cell lines PC3 and LNCaP. As expected, pioglitazone also inhibited tumor cell proliferation in the MCTS system. Further studies revealed that pioglitazone lowered the pH of the culture medium, decreased oxygen consumption and increased lactate secretion in both tumor cell lines. Other glitazones, troglitazone and ciglitazone, had similar effects. The combination of pioglitazone with 2-deoxyglucose, a potent inhibitor of glycolysis, had an additive effect on the inhibition of cell proliferation and led to MCTS disintegration. Our data propose a new mechanism of growth inhibition by pioglitazone through modulation of the tumor cell metabolism.

Key-words: Pioglitazone, Glitazones, Lactate, pH, Tumor cell proliferation, 2-Deoxyglucose