Manipulation of tumor metabolism for therapeutic approaches: ovarian cancer-derived cell lines as a model system.

Abstract:
Malignant transformation of cells is often accompanied by up-regulation of glycolysis-related enzymes and transporters, as well as a distortion of mitochondrial respiration. As a consequence, most malignant tumors utilize high amounts of glucose and produce and accumulate high concentrations of lactate, even in the presence of oxygen. This phenomenon has been termed 'Warburg Effect'. Here, we aimed at resolving the interrelation between tumor metabolism, reactive oxygen species, double strand DNA breaks and radio-resistance in ovarian cancer-derived cells. As a model system two ovarian cancer-derived cell lines, OC316 and IGROV-1, and its corresponding xenografts were used. First, the metabolic properties of the xenografts were tested to ensure that initial in vitro data might later be transferred to in vivo data. In parallel, three inhibitors of tumor cell metabolism, 2-deoxy-D-glucose, an inhibitor of glycolysis, oxamate, a pyruvate analogue and inhibitor of lactate dehydrogenase, and rotenone, a specific inhibitor of mitochondrial electron complex I, were tested for their effect on the metabolism and radio-sensitivity of the respective ovarian cancer-derived cell lines. We found that all three inhibitors tested led to significant changes in the tumor cell energy metabolism at
non-cytotoxic concentrations. Furthermore, we found that inhibition of tumor glycolysis by 2-deoxy-D-glucose in combination with rotenone decreased the radio-resistance at a clinically relevant radiation dose. This apparent radio-sensitizing effect appears to be based on an increased level of double strand DNA breaks 1 h and 24 h after gamma irradiation. Both cancer-derived cell lines maintained their metabolic properties, as well as their protein expression profiles and levels of reactive oxygen species in xenografts, thus providing a suitable model system for further in vivo investigations. A combination of metabolic inhibitors and reactive oxygen species-generating therapies, such as irradiation, may effectively enhance the therapeutic response in particularly metabolically highly active (ovarian) tumors.