

LACTATE AS A SIGNALING MOLECULE IN THE TUMOR MICROENVIRONMENT

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Tumor microenvironment is different from the normal one and influences the behavior of the cancer. Main characteristics of the tumor environment are hypoxia, hyperlactemia, hypercapnia and acidosis. Our work is focused on hyperlactemia and acidosis, which are caused by increased glycolysis followed by lactate fermentation even under conditions when oxygen is available. This phenomenon is called Warburg effect. Several reports showed that higher levels of tumor lactate correlate with a higher incidence of metastases, higher resistance to treatment, poor survival of patients and they increase the likelihood of disease recurrence. The aim of our work was to determine the effect of lactic acidosis on tumor cells sensitivity to oxidative stress. This feature was studied in the previously unexplored context of the lactate's ability to activate a master antioxidant and chemoprotective transcription factor Nrf2. We were investigating the viability of cancer cell which were cultivated in medium with different concentration of lactate anion and pH and treated with hydrogen peroxide. In addition, the nuclear translocation of Nrf2 protein was characterized with western blot and the expression of its target genes with real time PCR. It was found that the presence of lactate anion in acidic microenvironment increases the resistance of tumor cells to oxidative stress. Our preliminary data also show that the lactate treatment stimulates Nrf2 signaling pathway. This is, to our knowledge, the first demonstration of Nrf2 induction with lactate and of disjunction between the effects of lactate and acidosis on tumor cell resistance to stress.