ROLE OF METABOLISM IN CHEMORESISTANCE OF NEUROBLASTOMA CELLS.

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Introduction:
Metabolic profile of cancer cells reflects their altered bioenergetic requirements. Chemoresistance has been explained by changes in the genome of tumor cells that carry a particular mutation that is selected during the treatment. However, the rapidly acquired resistance to cytostatics is more likely to be attributed to the dynamics of non-genetic heterogeneity of the tumor population, which produces different phenotypic variants. The flexibility in using different energy pathways may indicate a survival adaptation to achieve a higher cellular fitness that might be also associated with chemoresistance.

Aims:
The aim of this study is to understand the connection between metabolic character and chemoresistance.

Materials and Methods:
Metabolism characterization was obtained from UKF-NB-4, UKF-NB-4CDDP, survivors CDDP, UKF-NB-4VCR, survivors VCR. The survivor cells have been created by a single high dose of cytostatics (vincristine -VCR/cisplatin -CDDP) and further cultivation in drug-free media for 3 weeks. We used Seahorse XF Glycolysis Stress Test for measuring glycolytic function and Mito Stress Test for measuring mitochondrial function in cells. The rate of O₂ consumption (OCR) can be assigned to OXPHOS and the rate of extracellular acidification (ECAR) to glycolysis. AlamarBlue viability test was performed to determine the differences in sensitivity of used cells to VCR/CDDP.

Results:
Our data suggests that metabolic changes occur as a result of chemotherapy drugs. We observed significantly lower glycolysis in UKF-NB-4 compared to respective resistant counterpart UKF-NB-4CDDP. This was also reflected in lower basal ECAR values that defined the glycolysis measure at resting state. Along with increased glycolysis, the chemoresistant cell also performed higher OXPHOS. To get an overall sight of the bioenergetics organization of the cells, a ratio of basal glycolysis vs. basal OXPHOS was generated. The results indicate that UKF-NB-4CDDP favor the OXPHOS pathway. VCR treatment did not result in any increase in metabolism, indicating the metabolic changes might be unique to platinum exposure.

Conclusions:
To understand the origin of acquired chemoresistance, we decided to analyze changes in metabolism of UKF-NB-4 and its derived resistant cell lines. The resistant cells seemed to switch to a high metabolically active phenotype, which enables them to survive a
chemotherapy insult better than the sensitive cell line. We observed that metabolic state influence chemoresistance. Understanding the cancer cells metabolism can lead to more effective treatment of tumors.

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