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Session E. Gastrointestinal (colorectal) cancer

E49 Glucose metabolism enzymes gene expression analysis and selective metabolic advantage in the clinical progression of colorectal cancer (CRC)

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Background: Invasive cancer cells mostly produce lactate even in the presence of sufficient levels of oxygen (aerobic glycolysis). This metabolic shift promote a survival advantage in proliferating cells, since it make them insensitive to transient or permanent hypoxia, it contributes to the production of nucleosides/aminoacids, and it constitutes a rapid way to produce energy. The analysis of altered expression of effectors causing redirection of glucose metabolism would improve our knowledge on a possible mechanism for chemoresistance, and secondary resistance to anti-angiogenic compounds. Also, it may optimize the current development of drugs targeting cancer metabolism. This background prompted us to analyze mRNA expression of key-enzymes involved in glycolysis in normal mucosa (NM), primary tumor (PT) and liver metastasis (LM) of CRC patients (pts) who underwent surgery (primary tumor resection and liver metastasectomy) and systemic therapy for advanced disease.

Materials and methods: Tissues of 50 chemotherapy-naive, non-diabetic CRC pts were retrospectively studied by RT-qPCR for mRNA expression of the following genes: hexokinase-1 (HK1) and 2 (HK2), embryonic pyruvate kinase (PKM2), lactate dehydrogenase-A (LDH-A), glucose transporter-1 (GLUT-1), voltage-dependent anion-selective channel protein-1 (VDAC1). The RT-qPCR DCt values (Cttarget–Ctreference) were used for calculating the expression level of each target gene with B2M and GUS adopted as reference genes. The primary end-point was to verify whether differences were detectable between tissues. T-test (Tt) and Wilcoxon test (Wt) were used for comparing DCt values between tissues (PT versus NM, LM versus NM, PT versus LM).

Results: In 49 assessable pts, essays repeated with B2M and GUS showed higher PT mRNA expression elevsl than NM for HK1 (Tt $p = 0.0001$; Wt $p = 0.0004$); LDH-A (Tt $p < 0.0001$, Wt $p < 0.0001$); PKM2 (Tt $p < 0.0001$, Wt $p < 0.0001$); GLUT-1 (Tt $p < 0.0001$, Wt $p < 0.0001$); VDAC1 (Tt $p = 0.0002$, Wt $p = 0.0004$). The same significant associations were found when comparing LM versus NM tissues. There was a borderline or not-significant trend for higher mRNA expression of these genes in LM versus PT tissues.

Conclusions.: The results indicate enhanced glucose uptake (GLUT-1), up-regulated aerobic glycolysis (HK, LDH, PKM2) and altered mithocondrial trafficking (VDAC1) in CRC. Additional analyses for association with RAS mutations status, progression-free survival after first-line chemotherapy plus bevacizumab and overall survival are ongoing.