

INCREASED AEROBIC GLYCOLYSIS IS ASSOCIATED WITH POOR OUTCOME AND SUPPRESSION OF APOPTOSIS IN HUMAN LIVER CIRRHOSIS AND HCC

Valeria Iansante¹, Pui Man Choy¹, Shilpa Chokshi², Roger Williams^{1,2}, Robert A. Anders³, Concetta Bubici⁴ and Salvatore Papa¹

Email: s.papa@researchinliver.org.uk

¹Cell signaling and Cancer Laboratory and ²Viral Hepatitis Laboratory, Institute of Hepatology, Foundation for Liver Research, London, UK. ³Division of Gastrointestinal and Liver Pathology, The Johns Hopkins University School of Medicine, Baltimore, USA. ⁴Division of Biosciences, Brunel University London, UK.

Background and Aims: Pro-inflammatory signalling in the liver promotes the appearance of a metabolic phenotype that involves the transition from mitochondrial respiration to aerobic glycolysis. It was demonstrated that this metabolic shift occurs during the transition from healthy and early stage of liver injury (NAFLD/NASH, ALD to late stage of disease (i.e. cirrhosis), and further escalates during HCC development [1,2]. This metabolic signature enables dividing cells to satisfy anabolic and energetic needs for biomass production and to suppress apoptotic signalling, which is consistent with increased compensatory hepatic cell proliferation typical of cirrhotic and HCC livers. However other studies in contrast have suggested that hepatocytes are unable to sustain glycolysis during late stage of chronic liver disease [3].

Methods: We used unbiased gene expression analyses of microarray datasets to investigate the expression of glycolytic genes in cirrhotic and HCC livers and correlated their expression with patient outcome. Furthermore, by using a combination of *in vitro* and *in vivo* analyses we have characterized the abilities of a novel anti-apoptotic gene to regulate aerobic glycolysis in liver cirrhosis and HCC.

Results: mRNA profiling showed significantly higher expression of glycolytic transcripts in cirrhotic and HCC livers compared to normal quiescent livers ($P < 0.05$). Up regulation of *Glut1*, *Hk1*, *Hk2*, *G6PI*, and *PFKL* was seen in HCC livers compared to their adjacent non-tumor tissues ($P < 0.001$). Notably, expression of enzymes regulating mitochondrial activity (*Pdha*, *Pdk*) was unchanged between non-tumor tissues and late stage of HCC. Moreover, up regulation of a novel anti-apoptotic gene positively correlated with increased expression of glycolytic transcripts in a group of cirrhotic patients prospectively classified as poor prognosis based on HCC development, and promotes the aerobic glycolysis of hepatoma cells.

Conclusions: In summary, our findings delineate a putative link between aerobic glycolysis and suppression of apoptosis that is an important part of the progression of cirrhosis to HCC. The identification of the mechanism regulating this link may lead to design new therapeutic strategies for human liver disease.

Reference:

- [1] Beyoğlu D, Idle JR. *J Hepatol.* 59: 842-858 (2013).
- [2] Kakazu E, *et al. Sci. Rep.* 3:3459 (2013).
- [3] Nishikawa T, *et al. J Hepatol.* 60: 1203-1211 (2014).