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Matrix Stiffness Promotes Hepatoma Cell Glycolysis and Migration Through YAP-Mediated Mechanotransduction

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Abstract: Hepatocellular carcinoma (HCC) is one of the most prevalent and lethal malignancies worldwide. Increased matrix stiffness of extracellular matrix (ECM) is commonly associated with HCC. During tumour formation and expansion, increasing glucose metabolism is necessary for unrestricted growth of tumour cells. Yet, the correlation between matrix stiffness and glucose metabolism in the development of HCC remains unknown. In this study, we aim to investigate the effect of matrix stiffness on glucose metabolism and migration of MHCC97L and HepG2 hepatoma cells, and explore the mechanotransduction involved in this process. Polyacrylamide hydrogels with stiffness gradients of 6, 25, 54 kPa were produced by changing the total monomer concentration of the hydrogel precursor solution. The migration of hepatoma cells was detected using wound healing and transwell assay. Western bolt was employed to detect the expression of key glycolytic enzymes, the glucose utilization and lactate production were assayed to evaluate the influence of matrix stiffness in hepatoma cell glycolysis. As a nuclear relay of mechanical signals exerted by ECM rigidity, Yes-associated protein (YAP) activity was assessed by subcellular localization and phosphorylation level. We found that hepatoma cell migration and glycolysis significantly increased with matrix stiffness increasing. Moreover, when glycolysis was inhibited by 2-Deoxyglucose, matrix stiffness had no significant effect on cell migration. In addition, stiffer matrix dramatically increased the activity of YAP. Further study confirmed that knockdown of YAP abrogated the migration and glycolysis of hepatoma cell plated on stiffer matrix. In conclusion, our study revealed that matrix stiffness increases hepatoma cell migration dependent on increasing glycolysis, and YAP-mediated mechanotransduction plays an important role in matrix stiffness-regulated hepatoma cell migration and glycolysis.

Keywords: Hepatocellular carcinoma; matrix stiffness; cell migration; glucose metabolism; mechanotransduction

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