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Low-level shear stress promotes migration of liver cancer stem cells via the FAK-ERK1/2 signalling pathway

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Abstract

Cancer stem cells (CSCs) are a small subpopulation of tumour cells that have been proposed to be responsible for cancer initiation, chemotherapy resistance and cancer recurrence. Shear stress activated cellular signalling is involved in cellular migration, proliferation and differentiation. However, little is known about the effects of shear stress on the migration of liver cancer stem cells (LCSCs). Here, we studied the effects of shear stress that are generated from a parallel plated flow chamber system, on LCSC migration and the activation of focal adhesion kinase (FAK) and extracellular signal regulated kinase1/2 (ERK1/2), using transwell assay and western blot, respectively. We found that 2 dyne/cm^2 shear stress loading for 6 h promotes LCSC migration and activation of the FAK and ERK1/2 signalling pathways, whereas treatment with the FAK phosphorylation inhibitor PF573228 or the ERK1/2 phosphorylation inhibitor PD98059 suppressed the shear stress-promoted migration, indicating the involvement of FAK and ERK1/2 activation in shear stress-induced LCSC migration. Additionally, atomic force microscopy (AFM) analysis showed that shear stress lowers LCSC stiffness via the FAK and ERK1/2 pathways, suggesting that the mechanism by which shear stress promotes LCSC migration might partially be responsible for the decrease in cell stiffness. Further experiments focused on the role of the actin cytoskeleton, demonstrating that the F-actin filaments in LCSCs are less well-defined after shear stress treatment, providing an explanation for the reduction in cell stiffness and the promotion of cell migration. Overall, our study demonstrates that shear stress promotes LCSC migration through the activation of the FAK-ERK1/2 signalling pathways, which further results in a reduction of organized actin and softer cell bodies.

Keywords: Cancer stem cells; Shear stress; Migration; FAK-ERK1/2 signaling pathway; Cell stiffness