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Decrease in expression of the mitoribosomal subunit, MRPL13, enhances hepatoma cell invasiveness via elevated claudin-1

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Impaired mitochondrial oxidative phosphorylation (OXPHOS) capacity, accompanied by enhanced glycolysis, is a key metabolic feature of cancer cells, but its underlying mechanism remains unclear. Previously, we reported that human hepatoma cells that harbor OXPHOS defects exhibit high tumor cell invasiveness via elevated claudin-1 (CLN1). In the present study, we show that OXPHOS-defective hepatoma cells (SNU354 and SNU423 cell lines) exhibit reduced expression of mitochondrial ribosomal protein L13 (MRPL13), a mitochondrial ribosome (mitoribosome) subunit, suggesting a ribosomal defect. Specific mitoribosomal translation inhibition with doxycycline and chloramphenicol, or siRNA-mediated MRPL13 knockdown decreased mitochondrial protein expression, reduced the oxygen consumption rate (OCR), and increased CLN1-mediated tumor cell invasiveness in SNU387 cells, which have active mitochondria. Interestingly, we also found that exogenous lactate treatment suppressed MRPL13 expression and OCR, and induced CLN1 expression. A bioinformatics analysis of the open RNA-Seq database from The Cancer Genome Atlas Liver Hepatocellular carcinoma (TCGA-LIHC) cohort disclosed a significant negative correlation between MRPL13 and CLN1 expression. Moreover, in LIHC patients with low MRPL13 expression, two oxidative metabolic indicators, pyruvate dehydrogenase B expression and the ratio of lactate dehydrogenase (LDH) type B to LDH type A, significantly and negatively correlated with CLN1 expression. This observation implied that the combination of elevated glycolysis and deficient MRPL13 activity is negatively linked to CLN1-mediated tumor activity in LIHC. These results suggest that OXPHOS defects may be initiated and propagated by lactate-mediated mitoribosomal deficiencies and that these deficiencies are critically involved in LIHC development.

Biography

Young-Kyoung Lee received her PhD in Biochemistry from Ajou University School of Medicine, Suwon, Korea. She is working as a Post-Doctoral Research Fellow at Ajou University School of Medicine. For about last ten years, her research has been focused on elucidation of molecular mechanisms of mitochondrial respiratory defects which are often observed in cancer, the retrograde signaling triggered by the respiratory defect and its relevance to cancer activities.

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