Regulation of mitochondrial respiration by LDHB suppression in hepatoma cell

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(ABSTRACT)
Aerobic glycolysis and mitochondrial dysfunction are distinctive metabolic hallmarks of solid tumor. However, it is unclear how these phenomena are developed during tumorigenesis. To maintain aerobic glycolysis, continuous generation of NADH by lactate dehydrogenase (LDH) is essential. Recently, we reported that LDH5 isozyme form by LDHB suppression is involved in increased glycolytic lactate production and mitochondrial respiratory defects in hepatoma cells. In this study, we aimed to investigate how LDHB suppression is linked with mitochondrial respiratory dysfunction. We have suggested that LDHB suppression might control mitochondrial respiration through posttranslational modification of respiratory related protein, thus, we have attempted to focus on pyruvate dehydrogenase (PDH) which is regulated by phosphorylation. Interestingly, LDHB knockdown effectively increased phosphorylation of PDH, indicating its inactivation. Treatment of lactate was increased PDH phosphorylation with lowering pH. This result implies that PDH phosphorylation is correlated with acidification, but is not lactate-specific event. Collectively, our results suggest that lactate-mediated PDH inactivation is the key mechanism to induce mitochondrial dysfunction in LDHB-suppressed hepatoma cell.

INTRODUCTION
Aerobic glycolysis in cancer cell

Lactic acid + pH 6.5
Lactic acid + pH 7.8

Lactate dehydrogenase (LDH)

What is the mechanism involved in LDHB suppression-mediated mitochondrial dysfunction?

- Alterations in expressions of respiratory proteins
- Alterations in metabolism for respiration
- Post-translational modification of respiratory-related enzymes

Pyruvate dehydrogenase(PDH)

RESULT

Figure 1. Decreased LDH expression-mediated lactate acidity in reversely associated mitochondrial respiratory activity.

Figure 2. LDH suppression is an upstream event of decreased mitochondrial respiration.

Figure 3. LDH knockdown induces PDH phosphorylation without HIF-1α induction.

Figure 4. LDH suppression-mediated PDH phosphorylation is regulated by PDH activation, but not through PDH induction.

Figure 5. Lactic acid increases PDH phosphorylation

Figure 6. LDH suppression-mediated lactate acidity induced PDH phosphorylation (b) and further amplified by lactate-associated acidification.

Figure 7. LDH suppression-induced PDH phosphorylation is mediated by HIF-1α activation.

Figure 8. Lactic acid delays cell growth with morphological changes.

CONCLUSION

REFERENCE