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Letter to the Editor

Effect of Lactate on Epigenetic Regulation in the Development of Hepatitis B Virus-related Hepatocellular Carcinoma

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Dear Editor,

Hepatitis B virus (HBV) is a hepatotropic virus that can establish a persistent and chronic infection in humans. Chronic hepatitis B (CHB) infection is associated with an increased risk of hepatic decompensation, cirrhosis, and hepatocellular carcinoma.[1] Emerging studies show that lactate, an end product of anaerobic glycolysis, has an important role in metabolism beyond energy production and is also a regulator of the tumor microenvironment (TME) and immune cell function.[2] It is noteworthy that lactate levels have been associated with mortality in patients, and large HBV surface proteins (LHBs) have been shown to reduce Pyruvate kinase M2 (PKM2) activity and thereby increase overall glucose consumption and lactate production in hepatocytes.[3]

Macrophage polarization is closely linked to changes in the cellular metabolic pathways and is classified as classically activated M1 and alternatively activated M2. M1 macrophages are pro-inflammatory macrophages that are induced by microbial products and can secrete a large number of pro-inflammatory cytokines. M2 macrophages are anti-inflammatory macrophages that secrete anti-inflammatory factors. Nowadays, it is accepted that M2 macrophages have a pro-tumor role, whereas M1 macrophages have anti-tumor activity.[4] Post-translational modification refers to the covalent and generally enzymatic modifications of proteins, and peptides after their biosynthesis.[5] Histone lysine lactylation (Kla) is a new epigenetic modification that regulates gene expression in macrophages.[6] Zhang *et al*.[7] discovered that histone Kla via the potential histone Kla writer protein p300 promotes the expression of M2-like genes in the late phase of M1 macrophage polarization after an inflammatory response, including arginase 1 (Arg1). Dysregulation of histone Kla by lactate disrupts the balance of gene transcription and causes diseases, including cancer.

We read with interest a recent article by Li *et al*.[8] on macrophage phenotypes and HBV infection that explained that HBV may promote M2 polarization of macrophages to impair the immune response of Type 1 T helper cells, resulting in persistent infection and disease progression.[8] On the other hand, studies by other researchers have shown that in M1 macrophages, lactate stimulates gene transcription through Kla to promote homeostasis.[7] With these findings, it can be hypothesized that HBV, via increasing lactate, leads indirectly to liver damage through Kla. The weakness of these studies is what is the relative contribution of lactate-dependent oxidation to bioenergetic metabolism versus lactate-derived metabolites such as acetyl-CoA in supporting M2 polarization and by how much? This letter should contribute to the point of view that our understanding of the increase of lactate in HBV infection may be useful in risk assessment. Nonetheless, the findings have raised many questions, and additional studies on lactate levels in HBV infection and their effects on Kla are necessary to discover novel therapeutic targets.

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Conflict of interest

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Author contributions

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Abbreviations: CHB, chronic hepatitis b; HBV, hepatitis b virus; Kla, histone lysine lactylation; LHBs, hepatitis B virus large surface protein; PKM2, Pyruvate kinase M2; TME, tumor microenvironment.

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