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Myeloid-derived suppressor cells are closely associated with disease progression in patients with HBV-related acute-on-chronic liver failure

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Background: MDSCs are a heterogeneous subset of immature myeloid cells with the potent ability to suppress T-cell responses through expression of increased levels of inducible nitric oxide synthase (iNOS), ROS and arginase and the shortage of L-arginine can inhibit T-cell proliferation through decreasing their expression of CD3 ζ-chain. The frequency and possible role of MDSCs are rarely studied in HBV-related ACLF (Acute-on-chronic Liver Failure) patients.

Methods: 25 HBV-related ACLF patients were enrolled in HBV-ACLF group, 15 of which were in early stage, 10 in middle and advanced stage. CHB group were consist of 26 mild to moderate patients and 16 severe patients, 18 healthy volunteers were admitted as healthy controls. The frequency of MDSCs and CD3 ζ-chain expression in CD8+T cells in three groups were detected by flow-cytometry. 8 patients with ACLF were enrolled and followed up for 4 weeks.

Results: MDSCs frequencies in peripheral blood mononuclear cells (PBMCs) were significantly increased in HBV-ACLF patients when compared with healthy controls and CHB patients. HBV-ACLF patients in middle to advanced stage had a higher frequency of MDSCs than those of early stage According to 4-week observation of ACLF patients, the peripheral MDSCs remained at high levels in the non-survival group, whereas the survival group displayed a gradual decline. CD3 ζ-chain expression was significantly down-regulated in $CD8^+$T cells of HBV-related ACLF patients as compared with CHB patients. Correlation analysis showed that MDSCs frequencies were positive correlated with ALT, TBIL, INR levels and MELD score.

Conclusion: Peripheral MDSCs are closely associated with disease progression in patients with HBV-related ACLF and they may serve as a possible predictor for short-term prognosis. MDSCs may suppress T-cell function through decreasing the expression of CD3 ζ-chain in CD8+T cells.

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Immuno-capture LC-MS/MS hybrid assay methodology in ADC bioanalysis

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Antibody drug conjugates (ADCs) are complex molecules composed of two pharmacologically distinct components, the cytotoxic payload and the antibody. The measurement of the payload molecules that are attached to the antibody *in vivo* is important for the evaluation of the safety and efficacy of ADCs, and can also provide distinct information compared to the antibody-related analytes. However, analyzing the antibody-conjugated payload is challenging and in some cases may not be feasible. The in vivo change in drug antibody ratio (DAR), due to deconjugation, biotransformation or other clearance phenomena, generates unique and additional challenges for ADC analysis in biological samples. We will present a novel hybrid approach with immuno-capture of the ADC, payload cleavage by specific enzyme, and LC-MS/MS of the cleaved payload to quantitatively measure the concentration of payload molecules still attached to the antibody in plasma. The hybrid conjugated payload assay was fully validated and successfully applied to IND-enabling toxicology studies. In addition, the payload molecule could undergo metabolism without deconjugation from the antibody, which will potentially affect the potency of the ADC. The selectivity of MS/MS detection offers easy and simultaneous measurement of the potential metabolism. The success of this assay prompted us to establish comprehensive hybrid methodology for the measurement of total antibody and conjugated antibody in fully supporting ADC bioanalysis, which will also be discussed in the presentation.

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