Abstracts

Factors Predicting In-Hospital Mortality in Patients Hospitalized for Liver Cirrhosis: A Five Years Retrospective Review in Cameroon

Chi Fru McWright*, Anutebeh Ephiseans, Ewane Edwin Nkwelle, Bokalli Francios Adrien, Teuwafeu Denis Georges, Luma Henry Namme, Faculty of Health Sciences, University of Buea, Cameroon; Buea Regional Hospital, Cameroon; Douala General Hospital, Cameroon

Background The global prevalence of liver cirrhosis has been on the rise, estimated at 4.5–9% from autopsy studies, projected at 50 million people affected in 2020 and ranked the 12th leading cause of death. However, data on studies evaluating the outcome of patients hospitalized for liver cirrhosis in SSA is scarce. We aimed to investigate the clinical and laboratory factors which predict in-hospital mortality in patients admitted for cirrhosis.

Methods This was a five years retrospective review of 183 cases hospitalized for liver cirrhosis between 1st January 2014 to 31st December 2018 in the medical units of two referral hospitals in Cameroon (figure 1). Independent variables investigated included: liver disease severity; clinical complications with severities; biomarker trends (using repeated measurements during hospitalization to compute the average, peak and minimum values for each patient) for serum sodium, potassium, creatinine, C-reactive protein, Neutrophil-to-Leukocyte ratio/NLR and Absolute Neutrophil Counts/ANC. Outcome investigated the in-hospital mortality, SPSS version 25.0 used to analyse data, logistic regression model to determine predictors of in-hospital mortality and significance set at P<0.05.

Results Cirrhosis accounted for 16 cases per 1000 hospitalizations, with a male-to-female ratio of 1:2 and a mean age of 53 (±18) years. Most cases were hospitalized for acute decompensation (93.4%) often presenting with ascites (76.5%) and hepatic encephalopathy/HE (41.5%). In-hospital mortality was 35.6%, peaked within the first five days, with factors associated including: HE (OR, 95%CI: 3.0, 1.6–5.6 P=0.001), high Western-Haven grade (P=0.009), hyperkalaemia (OR, 95%CI: 3.7, 2.7–4.7 P=0.011), elevated creatinine (OR, 95%CI: 3.0,2.3–3.8 P=0.004) and elevated absolute neutrophil count (OR,95%CI: 2.6, 1.8–3.5 P=0.016). Following adjustments, Hyperkalaemia (OR= 10, P=0.003) and elevated absolute neutrophil count (OR= 3.3, P=0.047) were the independent predictors.

Conclusions In-Hospital mortality is very high in cirrhosis; it depends on a combination of factors and is predicted independently by hyperkalaemia and elevated absolute neutrophil count. Thus physicians should frequently reassess their clinical, inflammatory and metabolic status.

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Switching off Immunosuppressive Myeloid Cells by Targeting Cell Cycle-Related Kinase Pathway: A NEW Strategy for Combination Immunotherapy

Jingying Zhou*, Joseph Jao-yiu Sung, Alfred Sze Lok Cheng. The Chinese University of Hong Kong, Hong Kong

Background The immune-checkpoint-blockade (ICB) therapy has produced promising and yet modest objective response...
rates in hepatocellular carcinoma (HCC), which has been attributable to the strong immunosuppressive tumor microenvironment (TME). As a key player in the TME, myeloid-derived suppressor cell (MDSC) shows potent T cell-suppressive activity that remarkably associates with poor prognosis and ICB resistance of cancer patients. While targeting MDSC can blunt T cell activity, a new approach is directed towards driving MDSC differentiation into antigen presentation cell which is crucial for T cell priming and activation. We have recently shown that hepatoma-intrinsic cyclin-dependent-kinase 20 (CDK20), or cell-cycle-related-kinase (CCRK) depletion diminishes MDSC-mediated immunosuppression leading to improved ICB efficacy (Gut 2018). As emerging evidence highlights the key roles of immune cell-intrinsic CDKs, we aimed to further explore the potentials of CCRK in immune cell identity.

Methods The expression profile of CCRK was determined in flow-sorted immune cells from tumor-bearing mice and HCC patients. Functional significance and molecular mechanisms of CCRK in MDSCs were conducted by gene knockdown in human blood-derived MDSCs, followed by mRNA and protein detection, qChIP-PCR and multi-colour flow cytometry. The MDSC differentiation and T cell suppression in tumorigenicity were validated in HCC mouse model with intratumoral MDSC injection.

Results We uncovered specific over-expression of CCRK in MDSCs but not lymphocytes from tumor-bearing mice and HCC patients. Notably, blockade of MDSC-intrinsic CCRK induced its differentiation into antigen-presenting macrophage, which amplified T cell responses in vitro and in vivo, resulting in reduced tumorigenicity. CCRK inhibition suppressed signal transducer and activator of transcription 3 (STAT3) signaling to revert E4-binding protein 4 (E4BP4)-dependent interleukin-10 (IL-10)/IL-12 imbalance and arginase 1 expression, thus blunting immunosuppression.

Conclusions Our findings demonstrate that targeting myeloid-intrinsic CCRK signal can amplify anti-tumor T cell responses. As we also showed CCRK overexpression in patient-derived MDSCs, our results not only unravel mechanistic insights in MDSC identity but also offer a novel therapeutic kinase-target for a combinational immunotherapy strategy for conferring durable eradication of solid tumors.

**Background** Hepatocellular carcinoma (HCC) is the fifth most prevalent cancer and the second leading cause of cancer deaths worldwide. Driven by the epidemics of obesity and diabetes, it is anticipated that non-alcoholic fatty liver disease (NAFLD) will become the most important cause of HCC. Emerging evidence suggests that metabolic and immune dysfunction are key features of NAFLD-associated HCC, my research aim to investigate the metabolic-immune dysregulation underlying NAFLD-HCC development. Here we show that aberrant cholesterolemia in the liver predisposes cancer development by reprograming the immunosurveillance microenvironment.

**Methods** Comprehensive immune profiling in a high-fat high-carbohydrate diet-induced NAFLD murine model was performed.

**Results** Our results revealed a specific reduction of cytolytic natural killer T (NKT) cells in the liver, which was negatively correlated with the elevated cholesterol level. Cholesterol-lowering drug Rosuvastatin reduced cholesterol level and restored NKT cell proportion and function, which subsequently suppressed the growth of orthotopically-implanted HCC tumor. Inhibition of cholesterol synthesis by an mTORC1/C2 dual kinase inhibitor Vistusertib (AZD2014), or lentiviral-mediated suppression of the mTOR pathway also showed similar effects. Notably, NKT inactivation by a specific CD1d receptor-targeting antibody abolished the anti-tumorigenic effects of both Rosuvastatin and Vistusertib, thus underscoring the crucial role of NKT in cholesterol-mediated hepatocarcinogenesis. We also showed a reduction of NKT cells and its negative correlation with cholesterol elevation in obese patients undergone bariatric surgery.

**Conclusions** Our study elucidates a new immunosuppressive role of cholesterol in establishing a pro-tumorigenic microenvironment. These findings explain why cholesterol-lowering drugs may reduce cancer incidence and provide new therapeutic strategies of revitalizing the immunosurveillance NKT cells for the intervention of NAFLD-associated HCC.

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