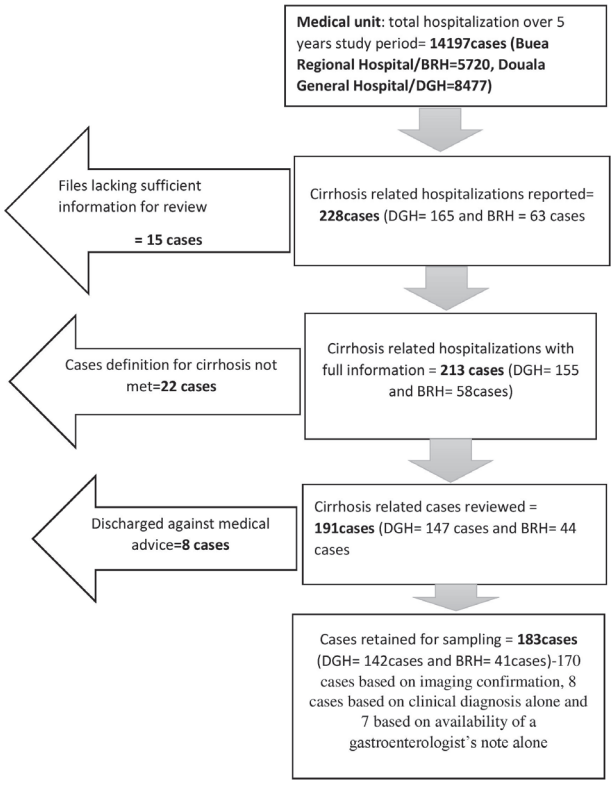
encephalopathy (HE) and infections respectively; 38.5% died at 90-days follow-up. Specific bacteria were found to be associated with HE [Bifidobacteriaceae,Coriobacteriaceae], sepsis [Veillonellaceae,Prevotellaceae], CTP>10 [Bifidobacteriaceae, Synergistaceae], MELD>25 [Dehalobacteriaceae,Turicibacteraceae] and death [Enterobacteriaceae,Peptococcaceae]. Significantly higher relative abundance(RA) of Lachnobacterium, Catenibacterium associated with HE at-admission while orally-represented bacteria were associated with infections at admission. Propionibacterium, Fusobacteria were associated with DF≥65 while Eubacterium, Capnocytophaga were associated with CTP. Enhydrobacter and Pediococcus were preferentially abundant post-steroid-therapy. Aerococcus was associated with post-treatment death. Prevotella was associated with survival post steroid. Upregulation of phenylpropanoid-biosynthesis (innate-immunity) in those without follow-up infections and glycerophospholipid-metabolism(cellular-integrity) in those who died were significant. Co-occurrence between Christensenella, Prevotella and mutual-exclusion between Megamonas, Citrobacter was associated with HE at admission. Mutual-exclusion between Coprococcus eutactus, Catenibacterium and Megamonas was associated with infections at admission while Enterococcus cecorum, Acinetobacter schindleri, Mitsuokella were associated with AKI at admission (figure 1).

Conclusions Specific gut-microbiota, their interactions and metabolites are associated with complications of SAH as well as outcomes with steroid-therapy. Advanced metagenomics-based precision-medicine as add-on treatments may be a novel therapeutic area for improving disease outcomes.



Abstract IDDF2020-ABS-0151 Figure 1 Flow chart demonstrating selection of sample population

IDDF2020-ABS-0151 FACTORS PREDICTING IN-HOSPITAL MORTALITY IN PATIENTS HOSPITALIZED FOR LIVER CIRRHOSIS: A FIVE YEARS RETROSPECTIVE REVIEW IN CAMEROON

[1]Chi Fru McWright*, [1]Anutebeh Ephiseans, [1]Ewane Edwin Nkwelle, [1]Bokalli Franciose Adrien, [2]Teuwafeu Denis Georges, [3]Luma Henry Namme. *[1]Faculty of Health Sciences, University of Buea, Cameroon; [2]Buea Regional Hospital, Cameroon; [3]Douala General Hospital, Cameroon*

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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 (figure1). 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 was 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), hyperkalemia (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.

IDDF2020-ABS-0178 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*

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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 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 I 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.

IDDF2020-ABS-0182 A NOVEL IMMUNOSUPPRESSIVE ROLE OF CHOLESTEROL IN NAFLD-ASSOCIATED HEPATOCARCINOGENESIS

Wenshu Tang*, Jingying Zhou, Weiqin Yang, Yu Feng, Heung Man Lee, Candice CH Lam, Anthony WH Chan, Simon KH Wong, Vincent WS Wong, Alice PS Kong, Alfred SL Cheng. *The Chinese University of Hong Kong, Hong Kong*

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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 cholesterol accumulation in the liver predisposes cancer development by reprogramming 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 casual 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 immunosurveillant NKT cells for the intervention of NAFLD-associated HCC.

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IDDF2020-ABS-0201 TARGETING HEPATOMA-INTRINSIC PPARγ SIGNALING OVERCOMES IMMUNE CHECKPOINT THERAPY RESISTANCE BY INFLAMING THE TUMOR MICROENVIRONMENT

Zhewen Xiong*, Stephen Chan, Jingying Zhou, Jianquan Cao, Joaquim SL Vong, Xuezhen Zeng, Yalin Tu, Yu Feng, Kevin Yip, Joseph JY Sung, Alfred Sze-Lok Cheng. *The Chinese University of Hong Kong, Hong Kong*

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Background Immune-checkpoint blockade (ICB) therapies by antibodies against programmed death 1 (PD1)/PD1 ligand 1 (PD-L1) axis have revolutionized the treatment paradigm for cancer. Although subsets of people exhibit durable responses, ICB resistance has increasingly been observed, especially in hepatocellular carcinoma (HCC). Here we utilized a single-cell RNA-sequencing (scRNA-seq) approach to elucidate the tumor-intrinsic mechanism underlying tumor immunosuppression and ICB resistance.

Methods We first recapitulated the clinical outcome of ICB resistance via repeated cycles of in vivo selection in orthotopic murine models of HCC. To investigate the tumor cell-extrinsic resistant factors, the myeloid and lymphoid immune populations were profiled by multi-color flow cytometry. To dissect hepatoma-intrinsic resistant signatures, we performed scRNA-seq from anti-PD-L1-treated tumors generated from parental or PD-L1R Hepa1-6 cells. The anti-tumor efficacy and immunophenotype of combined therapy with anti-PD-L1 antibody