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-0201 TARGETING HEPATOMA-INTRINSIC PPARY 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

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 tumour-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