Poster Presentations

01. Emerging concepts/new agents

P01.01 ISOLIQUIRITIGENIN ATTENUATED METASTATIC DEVELOPMENT OF PANCREATIC CANCER BY REGULATION OF THE TUMOR MICROENVIRONMENT AND REACTIVATION FROM CHEMORESISTANCE

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Background We have recently identified isoliquiritigenin (ISL), a flavonoid commonly found in licorice, as late-stage autophagy inhibitor during pancreatic cancer progression. In this study, we further investigated the anti-metastatic potential of ISL through regulation of the tumor microenvironment and metabolic pathway of gemcitabine chemoresistance.
Materials and Methods Cell migratory activity and invasiveness were determined in PANC1 and Mia PaCa2 pancreatic ductal adenocarcinoma (PDAC) cells by using Wound healing assay and 2-chamber Transwell matrigel invasion assay, respectively. Reactive oxygen species (ROS) generation was measured by a Total ROS Assay Kit using flow cytometry. Pan02 cells were inoculated to produce tumor xenograft in C57/BL6 mice. Cell surface staining was performed on samples from peripheral blood, spleen and tumor cells. Levels of different immune cells in the tumor tissues were determined by using immunofluorescence microscopy. Gene and protein expression of various biomarkers and metastatic mediators were determined by quantitative RT-PCR and Western immunoblotting, respectively.
Results ISL (12.5 or 25 μM) inhibited both migratory activity and invasiveness of PANC1 cells. ISL also downregulated the protein expression of epithelial-mesenchymal transition (EMT) biomarkers vimentin and Snail, as well as inhibited both gene expression and activities of pro-metastatic biomarkers MMP-2 and MMP-9 in tumor tissues. Besides, ISL increased ROS level in PANC1 and MiaPaCa2 cells, which could explain the subsequent inhibition of late-stage autophagy being observed earlier. In the tumor microenvironment, ISL decreased the number of myloid-derived suppressor cells (MDSC) while increased the number of CD4 and CD8 T cells in the spleen, tumor tissues and peripheral blood of mice xenograft. ISL impaired the M2 polarization of macrophage in tumor tissues as indicated by decrease in expression of CD206, the marker of M2 macrophage phenotype. INF-γ increased the protein expression of both p-STAT1 and STAT1 in PANC1 cells at concentrations that did not induce cytotoxicity, which alleviated the growth-inhibitory and proapoptotic effects of ISL in PANC1 cells. Alternatively, ISL decreased both phosphorylation and nuclear translocation of STAT1 in PANC1 cells, whereas the inhibition of STAT1 activation in PANC1 cells by ISL could be attenuated by INF-γ. Our latest findings have unveiled that modulation of STAT1 by ISL involves Rac1-p38-CREB signaling. Despite this, ISL facilitated inhibition of RRM1 protein expression, while it upregulated the gene expression of dCK and hENT1 in MiaPaCa2 cells. ISL had exhibited synergistic cell growth inhibition of PANC1 and Mia PaCa2 with gemcitabine.
Conclusions Our results reveal that ISL attenuated metastatic development of pancreatic cancer by reprogramming of the tumor immunity and reactivation from gemcitabine chemoresistance.

J.K. Ko: None.

P01.02 BIUX2X2

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Background Patients with pancreatic ductal adenocarcinoma (PDAC) are at a higher infection risk for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and have a worse outcome, but the underlying detailed reasons have not yet been elucidated.
Materials and Methods We performed a multicohort analysis Using sequencing data from bulk and single-cell RNA derived from tissue, blood, and nasopharyngeal samples from PDAC and COVID-19 patients.
Results We identified upregulations of the crosstalk genes (CTGs) EPSTI1, USP18, NUSAP1, ANP32E, and PSMC2 in both diseases. These CTGs are expressed mainly by proliferating CD4, CD8, and natural killer (NK) cells. USP18 and EPSTI1 are associated with impaired interferon (IFN) signalling in patients who died from SARS- CoV-2-infection, whereas surviving COVID-19 patients had higher IFN scores. Dysregulated IFN signalling also correlated with high susceptibility of PDAC patients to SARS-CoV-2 infection with high mortality. Based on the identified CTG signature and clinicopathological characteristics, we designed a nomogram and found that it predicts the overall survival of PDAC patients even more accurately than the conventional nomogram.
Conclusions Therefore, PDAC and COVID-19 share regulatory mechanisms, which together exacerbate the already weakened immune response in PDAC and worsen prognosis. The evaluation and therapeutic targeting of the identified gene signature could contribute to the success of personalized treatment of SARS-CoV-2-infected PDAC patients.

S.S. Han: None.

P01.03 ENHANCING NK CELL CYTOTOXICITY AGAINST TUMOR CELLS WITH A NOVEL SELF-DELIVERING RNAI COMPOUND TARGETING CBL-B

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Background NK cells are the body's first line of defense against cancer, able to recognize and kill tumor cells without having been exposed to the tumor cell previously. Unlike T cells, NK cells do not induce graft-versus-host disease. Therefore, using NK cells in adoptive cell therapy (NK-ACT) holds promise as a true 'off-the-shelf' cellular immunotherapy for cancer, with the potential to circumvent many of the hurdles associated with autologous cell therapies. NK-ACT has demonstrated potential against hematological cancers, but the activity of NK cells in ACT should be enhanced to improve clinical efficacy. Cbl-b, an E3 ubiquitin ligase, is an important gatekeeper, which limits NK cell activation. In NK cells, Cbl-b is activated and stabilized through inhibitory receptor