Recent updates of precision medicine—marker-guided therapy and immune checkpoint blockage

去邪與扶正-今日的精準醫學

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Poly (ADP-ribose) polymerase (PARP) inhibitors have emerged as promising therapeutics for many diseases, including cancer. My group showed that combination of c-Met and PARP1 inhibitors synergized to suppress growth of breast cancer cells *in vitro* and xenograft tumor models (***Nature Medicine*** 22:194, 2016). We are working with clinicians at MD Anderson and initiate clinical trials using combinational therapy of PARP and c-MET inhibitors.

Anti-PD-1/PD-L1 therapy is a promising approach in cancer therapy. We showed that glycosylation of PD-L1 is required for its protein stability and interaction with PD-1 (***Nature Communications*** 7:12632, 2016). Furthermore, we developed an effective combination therapy by metformin-activated AMPK kinase to downregulate PD-L1 through alteration of glycosylation of PD-L1 and functionally mimics anti-PD-L1 to block PD-L1/PD-1 interaction. It exhibited a highly potent synergistic effect of combination therapy of metformin, a drug that has been treated patients with diabetes and anti-CTLA4 in different syngeneic mouse models. The therapeutic efficacy could reach to the survival rate of 50-70% in different syngeneic mouse models which were treated by this combination therapy (***Molecular Cell*** 71:606, 2018). We demonstrated that epithelial-mesenchymal transition (EMT) enhances PD-L1 in cancer stem-like cells (CSCs) by the EMT/β-catenin/STT3-PD-L1 signaling axis. Etoposide, a commonly used anti-cancer chemotherapy drug is able to suppress this signaling axis, resulting in downregulation of PD-L1 to sensitize cancer cells to anti-Tim 3 therapy (***Nature Communications*** 9:1908, 2018). We identified two mechanisms in HCC to develop effective combination therapy with immunotherapy (***Gastroenterology*** 156:1849, 2019 & ***Journal of Clinical Investigation*** in press, 2019). We identified TNFα as a major factor triggering cancer cell immunosuppression against T cell surveillance via stabilization of programmed cell death-ligand 1 (PD-L1) (***Cancer Cell*** 30:925, 2016). To this end, in collaboration with StCube Pharmaceuticals Inc., we have developed monoclonal antibodies against glycosylation-specific PD-L1. Impressive therapeutic effect was observed through antibody-drug-conjugate approach (***Cancer Cell*** 33:187, 2018). PD-L1 is heavily glycosylated which makes it difficult to accurately detect PD-l1 expression and has been a puzzle to use PD-L1 expression to stratify patients for treatment. Lately, we developed a method to resolve this issue by removing the glycan moieties from cell surface antigens via enzymatic digestion. We demonstrated that improved PD-L1 detection after deglycosylation is associated with response to anti-PD-1/PD-L1 therapy as well as Increased PD-L1 signal after deglycosylation is beneficial to therapeutic selection. We also showed that antigen retrieval by protein deglycosylaton improves predictive ability of PD-L1 as a biomarker for immunotherapy. (***Cancer Cell*** *in press* 2019).

If time allows, this talk will include our recent discoveries on developing therapies for lung or pancreatic cancers (***Cancer Cell*** 34:9549, 2018 ***& Cancer Cell*** 33:752, 2018) as well as role of exosome-PD-L1 and PD-L1 palmitoylation in T-cell killing (***Cell Res*** 28:862, 2018; ***Cell Res*** 29:83, 2019); these finding could provide new alternative approaches to improve anti-PD-L1/PD-1 therapeutic efficacy.