Marker-guided effective therapy (Mget)

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Abstract

Cancer therapy has moved into a new era, including mechanism-driven marker-guided target therapy and immune therapy. Anti-PD-1/PD-L1 therapy is a promising immune therapy for multiple cancer types. Glycosylation of PD-L1 is required for its protein stability and interaction with PD-1 (Nature Comm 2016). Impressive therapeutic effect of developed glycosylation-specific PD-L1 mAb was observed through antibody-drug-conjugate approach (Cancer Cell 2018a & Cancer Res 2020). Through identifying potential targets, we developed marker-guided effective therapy (Mget) to enhance therapeutic efficacy and/or overcome drug resistance by combination therapy with immune checkpoint therapy, including metformin (Mol Cell 2018), c-MET inhibitors (Gastroenterology 2019); and targeting IL-6/JAK1 pathway (J Clin Invest 2019), Galectin-9 (Nature Comm 2021, IJBS 2023a), Tyro 3 (J Clin Invest 2021). Several PARP inhibitors have been approved to treat cancer patients with BRCA mutation and/or homologous recombination defective tumors, we also investigate the mechanisms inducing resistance to PARP inhibitors and develop marker-guided combination therapy to overcome the resistance. The goal is to use identified markers to stratify patients for the right combination therapy. These include reports on c-Met, ALK and GSDMC (Nature Medicine 2016; Nature Cancer 2022 & JCI 2024). This talk will also include our discoveries on novel therapy overcoming resistance to EGFR TKI in lung cancer (Cancer Cell 2018b , clinical trial, NCT06071013 is ongoing) and other caner types as well as a new methodology to retrieve antigen by protein de-glycosylaton that improves predictive ability of PD-L1 as a biomarker for immunotherapy. (Cancer Cell 2018b, Cancer Cell 2018c, Cancer Cell 2019, AJCR 2022a, Nature Reviews Clinical Oncology 2022, Nature, 2020, Nat. Cell Biol 2020; Mol Cell 2021, IJBS 2023a,b,c, Nature Comm 2024). We will also share with our recent unpublished data for markers-guided effective therapy using novel serum markers (ChiCTR2100054794, submitted). All efforts are focused on mechanism-driven marker-guided effective therapy in a hope to benefit cancer patients.