Poly (ADP-ribose) polymerase (PARP) inhibitors have emerged as promising therapeutics for many diseases, including cancer, in clinical trials. Three PARP inhibitors have been approved by the FDA to treat ovarian cancer with (olaparib andrucaparib)or without BRCA mutations (niraparib). BRCA1 and BRCA2 play essential roles in repairing DNA double strand breaks, and a deficiency of BRCA proteins sensitizes cancer cells to PARP inhibition. My group recently demonstrated that receptor tyrosine kinase c-Met associates with and phosphorylates PARP1 at Tyr907. Phosphorylation of PARP1 Tyr907 increases PARP1 enzymatic activity and reduces binding to a PARP inhibitor, thereby rendering cancer cells resistant to PARP inhibition. Combining c-Met and PARP1 inhibitors synergized to suppress growth of breast cancer cells in vitro and xenograft tumor models. Similar synergistic effects were observed in a lung cancer xenograft tumor model. These results suggest that PARP1 pTyr907 abundance may predict tumor resistance to PARP inhibitors, and that treatment with a combination of c-Met and PARP inhibitors may benefit patients bearing tumors with high c-Met expression who do not respond to PARP inhibition alone (Nature Medicine 22:194-201, 2016).

Extracellular interaction between programmed death ligand-1 (PD-1) and programmed cell death protein-1 (PD-1) leads to tumor-associated immune escape. Here, we show that the immunosuppression activity of PD-L1 is stringently modulated by ubiquitination and N-glycosylation. We identified glycolgen synthase kinase 3b (GSK3b) as a novel protein that interacts with PD-L1 and can induce phosphorylation-dependent proteasome degradation by b-TrCP. We also demonstrate that epidermal growth factor (EGF) stabilizes PD-L1 via GSK3b inactivation in basal-like breast cancer (BLBC). Inhibition of EGF signaling by gefitinib destabilizes PD-L1, enhances antitumor T cell immunity and therapeutic efficacy of PD-1 blockade in syngeneic mouse models. Together, we demonstrated a novel interchange between glycosylation and phosphorylation regulating ubiquitination and degradation of PD-L1. This regulatory event is critical for BLBC cells that escape immune surveillance via PD-L1/PD-1 interaction. Importantly, inhibition of EGF-mediated PD-L1 stabilization enhances a therapeutic efficacy of PD-1 blockade to promote tumor-infiltrating cytotoxic T cell immune response. Thus, targeting PD-L1 stabilization provides a novel strategy to combat BLBC-mediated immunosuppression and may potentially apply to other cancer types (Nature Communications 7:12632, 2016). In a most recent study, 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 ab-drug-conjugate approach and a manuscript is in press in Cancer Cell.