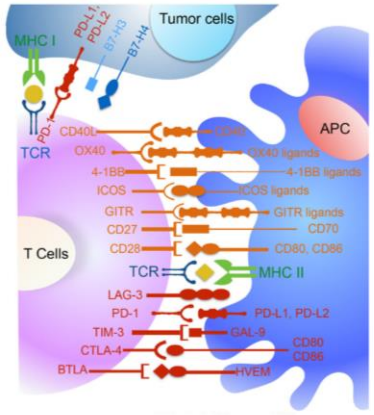
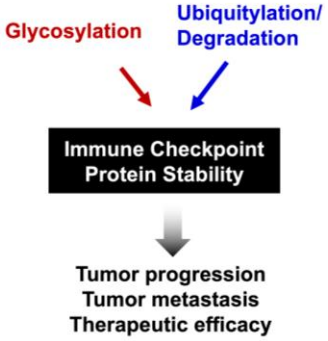
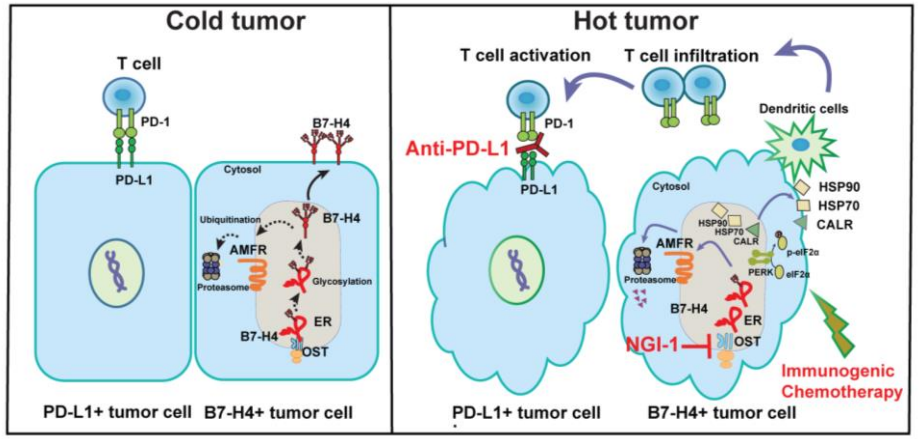
The Role of Posttranslational Modifications in Regulating Immune Checkpoint Function







Recent studies have implied that the immune checkpoint proteins are tightly regulated by posttranslational modifications (PTMs) such as ubiquitylatin and glycosylation. PTMs are involved in regulating various aspects for immune checkpoint proteins, including their protein quality control, protein trafficking, protein stability and the immune checkpoint function on cell membrane. Our lab currently focuses on the mechanisms that regulate immune checkpoint function by PTMs and searches for new strategy for cancer therapy specifically from the view of the regulation of immune checkpoint protein by PTMs.

Despite the widespread use of immunotherapy, the poor clinical response by immune-cold tumors is a current challenge. Triple negative breast cancer (TNBC) is the most aggressive mammary carcinoma subtype. Although a PD-L1 inhibitor has been FDA approved for the treatment of metastatic TNBC, the majority of TNBC patients show limited responses, particularly when their tumors are “cold” or “non-inflamed”. In contrast with “hot” tumors, these immune-cold tumors are characterized by a scarcity of T lymphocyte infiltration, commensurate with their failure to elicit anticancer immunity. Our endeavor to identify suitable targets for improving anticancer immune responses against TNBC therapy has drawn our attention to B7-H4.

Using combinatorial approaches, we unravel a novel regulatory mechanism by which B7-H4 protein turnover is governed by asparagine (N)-linked glycosylation. N-linked glycosylation is a co- and post-translational modification important for protein stability, folding, trafficking, and physiological function. Glycosylation of B7-H4 catalyzed by specific glycosyltransferases (STT3A and UGGG1) antagonizes the B7-H4 ubiquitination by E3 ligase autocrine motility factor receptor (AMFR), thereby preventing the degradation of B7-H4 and hence stabilizing the protein. Abundant B7-H4 can inhibit the phosphorylation of eIF2α, CALR exposure, and cancer cell immunogenicity. We designed a strategy for inhibiting the oligosaccharyltransferase (OST) complex that stabilizes B7-H4, thus reducing its expression and enhancing the immunogenicity TNBC cells in the context of immunogenic cell death-eliciting chemotherapy and PD-L1-targeting immunotherapy. We are currently under the process to develop new small molecule inhibitor that could specifically target the glycosylated B7-H4 for cancer treatment.