Abstract Impact

Chemotherapy is the only available treatment for many breast cancer patients, but many respond poorly; our research identifies mechanisms of resistance to chemotherapy, and novel therapeutic strategies to overcome this resistance.

Objectives/goals

Patients with *TP53* wild-type (WT) breast cancers have extensive residual disease and dismal survival after chemotherapy because they enter a state of arrest termed senescence, thus avoiding cell death. We aim to reveal how senescent cells in residual disease evade immune clearance.

Methods/study population

Chemotherapy-treated/untreated MMTV-*Wnt1* mammary tumors were harvested, fixed, sectioned, and stained to assess expression of various markers using confocal microscopy. RNA-seq was used to assess the immune contexture after chemotherapy in p53 WT MMTV-*Wnt1* mammary tumors and human breast cancer cell lines. GSEA was performed to identify enriched pathways following chemotherapy treatment. For efficacy studies, syngeneic mice were orthotopically transplanted with MMTV-*Wnt1* tumors and received IP injections of 4 mg/kg doxorubicin daily for 5 consecutive days. Mice then received IP injections of 200μg anti-PD-L1 or IgG control every 72hrs for 3 doses. Tumors were measured using digital calipers.

Results/anticipated results

Cells in post-chemotherapy residual disease were enriched for antigen presentation ($p<0.25$ FDR). To determine why tumors escaped immune clearance despite evident antigenicity, we examined factors involved in immune suppression. We found a remarkable elevation of PD-L1 following induction of senescence in residual disease of chemo-treated p53 WT but not mutant tumors. Unlike other senescence genes, PD-L1 expression persisted in the relapsed tumor, suggesting the cells that proliferated to drive relapse were those with high PD-L1 expression. MMTV-*Wnt1* mice treated with chemo+anti-PD-L1 had a superior response including cases of complete eradication compared to mice given chemo+IgG ($p=0.022$).

Discussion/significance of impact

Our data suggest a mechanism for persistence of residual disease in chemotherapy treated p53 WT tumors: PD-L1 upregulation induced in senescence. Treating residual disease with anti-PD-L1 significantly improved outcome in a model of breast cancer that respond the worst to treatment. Our data suggest that patients with *TP53* WT breast cancers treated with chemotherapy are most likely to benefit from treatment with anti-PD-L1, highlighting p53 status as a novel predictive biomarker in immunotherapy response. Because the efficacy of anti-PD-L1 in breast cancer is unimpressive, identifying patients that respond best is a priority.