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**Testing novel immune checkpoint therapy combinations targeting CD47 in an immune-competent tumor organoid platform of triple-negative breast cancer.**

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Cancer immunotherapies, such as immune checkpoint blockade, are currently used in the clinic to activate a patient's immune system to specifically destroy cancer cells. While these therapies show remarkable efficacy, only 7% of metastatic triple-negative breast cancer (TNBC) patients respond to these treatments. Therefore, better strategies and models to stimulate immunogenicity within TNBC tumors are needed to enhance patient response. CD47 is an integral membrane protein that is overexpressed in cancer cells, allowing them to bypass antitumor immunosurveillance from innate immune cells when engaged by its counterreceptor signal regulatory protein alpha (SIRPα)**.** Conversely, CD47 is also expressed in T cells, causing decreased activation, immunosuppressive phenotype differentiation, and cell death when engaged by the ligand thrombospondin-1 (TSP1). Additionally, disease progression in TNBC patients is associated with the co-expression of CD47 and the immune checkpoint protein, programmed death-ligand 1 (PD-L1). Therefore, our lab is interested in determining whether targeting CD47 sensitizes TNBC tumors to PD-L1 therapy in murine models and tumor organoid platforms. Our data show that CD47 expression is elevated in biopsies of TNBC patients. Furthermore, CD47 blockade resulted in a significant decrease in tumor volume and weight in an orthotopic murine EMT-6 TNBC model. A further reduction in tumor burden was observed when combined with immune checkpoint blockade therapy against PD-L1. This decrease in tumor burden is correlated with increased intratumoral CD8+ T cells, which may have enhanced antitumor function due to increased gene and protein expression of granzyme B. The enhancement of effector cytotoxic function was associated with increased T cell bioenergetics with CD47 blockade. We then used a tumor organoid platform to investigate tumor sensitization mechanisms by targeting CD47. By embedding murine TNBC tumor tissue and antigen-specific AH1 $CD8^+$ T cells in a specialized ECM mimicking hydrogel, organoids were constructed. When CD47 was targeted, enhanced CD8+ T cell cytolytic capacity was observed within the organoid due to increased IFNγ and granzyme B release. These results were consistent with our *in vivo* observations suggesting that the organoid platform may be a suitable strategy to test therapeutic responses. Overall our data indicate that targeting CD47 may enhance T cell bioenergetics and TNBC tumor immunogenicity, enhancing response to PD-L1 therapy and potentially improving overall patient survival.

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