Advances in early detection and treatment have led to a decrease in cancer-related mortality; consequently, by the year 2030, there will be over 20 million cancer survivors in the United States. Anthracycline-based treatment regimens are currently essential for managing triple-negative breast cancer. Patients treated with doxorubicin (DOX) often exhibit cardiovascular morbidity due to cumulative dose-dependent cardiotoxicity. Novel strategies are needed to overcome anthracycline-induced cardiotoxicity in the increasing number of survivors of breast cancer. Activation of the CD47/Thrombospondin-1 (TSP1) signaling axis impacts the progression of heart failure with reported increased TSP1 levels following myocardial infarction. Therefore, we examined the potential of CD47 blockade as a strategy to prevent chemotherapy-induced cardiac injury. CD47 is a transmembrane protein that plays a role in cell fate during cellular stress through its interaction with TSP1. Our data in a syngeneic orthotopic breast cancer model shows that CD47 blockade using an in vivo anti-sense phosphodiesterase morpholino (PMO) preserved ejection fraction, fractional shortening, and cardiac output when compared to DOX treatment. RNA sequencing was performed on the hearts of control and CD47 PMO-treated mice to determine a potential cardioprotective mechanism. Gene set enrichment analysis (GSEA) showed significant positive enrichment for metabolic pathways including pyruvate metabolism (NES= 2.3, p<0.002), fatty acid oxidation (NES= 2.53, p<0.003), oxidative phosphorylation (NES=2.0, p<0.01) while negative enrichment was observed in pathways related to cytokine receptor interaction (NES= -2.2, p<0.002) and extracellular matrix receptor (ECM) interaction (NES= -2.6, p<0.05). During cardiac insult, metabolic flexibility of cardiomyocytes results in metabolic reprogramming from fatty acid oxidation to a glycolytic mechanism to overcome injury. Thus, DOX-associated cardiotoxicity may be mediated by an increase in TSP1 and a decrease in glycolysis, leading to the inability to overcome acute cellular stress. In-vitro cellular bioenergetics analysis revealed that TSP1 caused a dose-dependent reduction in glycolytic flux and glycolytic capacity in cardiac cells. This analysis, coupled with preserved cardiac cell viability in cells treated with CD47 PMO in the presence of DOX, suggests that TSP1 may act through CD47 to prevent cardiac cell metabolic reprogramming needed to overcome injury. Overall, our studies suggest that the TSP1/CD47 axis may be central to the interplay of ECM proteins and metabolism to preserve cardiac tissue integrity; thus, targeting this pathway may prevent the onset of chronic cardiac disease due to chemotherapy in cancer patients.