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Anti-CD47 immunotherapy increases glycolysis in cardiomyoblast as a protective mechanism from chemotherapy-related cardiotoxicities.

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Abstract

Due to advances in early detection and treatment, cancer-related mortality has decreased, and by 2030, there will be 22 million cancer survivors in the United States. This is a positive milestone, but the incidence of cancer-therapy-related cardiovascular side effects has increased. Patients with triple-negative breast cancer (TNBC) are particularly susceptible to the off-target effects of chemotherapy due to treatment relying on systemic cytotoxic chemotherapy. Therefore, novel strategies are needed to overcome chemotherapy-induced cardiac injury. One such novel strategy is CD47 blockade. CD47 is a transmembrane protein that plays a role in cell fate during cellular stress through its interaction with Thrombospondin-1. Our group and others have demonstrated targeting CD47 enhances innate and adaptive immune responses against tumors. CD47 expression increases with chemotherapy administration in tumor cells, and we show that expression is also elevated in cardiomyoblasts. This increased expression is associated with chemotherapy-induced cytotoxicity in cardiac cells. However, CD47 blockade results in preserved cardiomyoblast viability after chemotherapy treatment. Furthermore, *in vivo* studies shows that blockade of CD47 prevents cardiac dysfunction associated with doxorubicin administration in TNBC tumor-bearing mice. We examined cellular energetics to determine the protective mechanism. Glycolysis rate was measured in H9C2 rat cardiomyoblasts to determine if glucose metabolism is affected by CD47 blockade in tumor-conditioned media versus non-conditioned media with the addition of doxorubicin. CD47 blockade increased glycolysis and glycolytic capacity when cells are under stress induced by doxorubicin and conditioned media. Therefore, increasing glycolysis under stress may allow cells to overcome insult, increase cardiac viability, and preserve cardiac function. Thus, strategies targeting CD47 should be considered in the clinic to prevent cancer therapy-related cardiotoxicities and improve patient quality of life.