TICAGRELOR INHIBITS PLATELET-TUMOR CELL INTERACTIONS AND METASTASIS IN HUMAN AND MURINE BREAST CANCER

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Activated platelets promote the proliferation and metastatic potential of cancer cells, and this activation is primarily mediated through ADP engagement of purinergic $P2Y_{12}$ receptors on platelets. In this study, we examined the potential of the reversible $P2Y_{12}$ inhibitor ticagrelor, an agent used clinically to prevent cardiovascular and cerebrovascular events, to reduce tumor growth and metastasis. *In vitro*, MCF-7, MDA-MB-468, and MDA-MB-231 human mammary adenocarcinoma cells demonstrated decreased interaction with ticagrelor-treated platelets compared to untreated platelets. Prevention of tumor cell–platelet interactions through pre-treatment of platelets with ticagrelor did not improve natural killer cell-mediated tumor cell killing of K562 myelogenous leukemia target cells. Ticagrelor decreased the expression of P-selectin on human platelets, but had no effect on proliferation of 4T1 mouse mammary carcinoma cells co-cultured with platelets. In an orthotopic 4T1 breast cancer model, ticagrelor (10 mg/kg), but not clopidogrel (10 mg/kg) or saline, resulted in reduced metastasis and improved survival, although ticagrelor treatment did not have an impact on primary tumor volume. Ticagrelor treatment was associated with a marked reduction in tumor cell–platelet aggregates in the lungs at 10, 30 and 60 min post-intravenous inoculation. Taken together, these findings suggest a role for $P2Y_{12}$-mediated platelet activation in promoting metastasis and provide support for the use of ticagrelor in the prevention of breast cancer spread.