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Abstract
Degradation of the extracellular matrix (ECM) plays a critical role in the formation of tumors and metastasis and has been found to correlate with the aggressiveness of tumor growth and invasiveness of the cancer. Ascorbic acid, which is known to be essential for the structural integrity of the intercellular matrix, is not produced by humans and must be obtained from the diet. Cancer patients have been shown to have very low reserves of ascorbic acid. Our main objective was to determine the effect of ascorbate supplementation on metastasis, tumor growth and tumor immunohistochemistry in mice unable to synthesize ascorbic acid (gulo KO) when challenged with melanoma B16FO or breast 4T1 cancer cells. Gulo KO female mice 36-38 weeks of age were deprived of or maintained on ascorbate in food and water for 4 weeks prior to and 2 weeks post intraperitoneal (IP) injection of 5 x105 B16FO murine melanoma cells or to injection of 5x105 4T1 breast cancer cells into the mammary pad of mice. Ascorbate-supplemented gulo KO mice injected with B16FO melanoma cells demonstrated significant reduction (by 71% ($p=0.005$) in tumor metastasis compared to gulo KO mice on the control diet. The mean tumor weight in ascorbate supplemented mice injected with 4T1 cells was reduced by 28% compared to tumor weight in scorbutic mice. Scorbutic tumors demonstrated large dark cores, associated with increased necrotic areas and breaches to the tumor surface, apoptosis and MMP-9, and weak, disorganized, or missing collagen I tumor capsule. In contrast, the ascorbate supplemented group tumors had smaller fainter colored cores and confined areas of necrosis/apoptosis with no breaches from the core to the outside of the tumor and a robust collagen I tumor capsule. In both studies, ascorbate supplementation of gulo KO mice resulted in profoundly decreased serum Inflammatory cytokine IL-6 (99% decrease, $p=0.01$ in the B16F0 study and 85% decrease, $p= 0.08$ in the 4T1 study) compared to the levels in gulo KO mice deprived of ascorbate. In the B16FO study, ascorbate supplementation of gulo KO mice resulted in profoundly decreased serum VEGF (98% decrease, $p=0.019$ than in the scorbutic gulo KO mice. As expected, mean serum ascorbate level in ascorbate restricted mice was 2% ($p<0.001$) of the mean ascorbate level in supplemented mice. In conclusion, ascorbate supplementation hindered metastasis, tumor growth and inflammatory cytokine secretion as well as enhanced encapsulation of tumors elicited by melanoma and breast cancer cell challenge in gulo KO mice.

Key words:
ascorbate; gulo KO mice; metastasis, tumor growth; melanoma B16F0, breast cancer 4T1, collagen I and IV, MMP-9, apoptosis, IL-6

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