Title: Heart- Spleen-Tumor: The Unexplored Connections in Cardio-Oncology

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Introduction: Doxorubicin (DOX) is an efficacious antineoplastic agent; however, its clinical application is often limited by its cardiotoxic effects. The immune system, particularly the spleen, plays critical roles in cardiac remodeling and tumor progression. However, the impact of the spleen on the cardiotoxic and tumor-suppressive effects of DOX remains unexplored.

Methods: Tumor-free and EL4 lymphoma tumor-bearing intact C57BL/6N male mice were administered saline or DOX (4mg/kg/day) intraperitonially for 6 days, starting when the EL4 tumors became palpable. To determine the impact of the spleen, the same experiment was repeated in sham and splenectomized mice. In all experiments, tumor growth was monitored daily, and cardiac function was measured on the 7th day followed by necropsy on the 8th day. Gene expressions of cardiotoxicity and inflammatory markers in the heart were determined by real-time PCR.

Results: DOX effectively inhibited tumor growth but significantly reduced cardiac output and spleen weight, with a strong negative correlation observed between these two parameters. DOX also caused significant upregulation of cardiotoxicity and inflammatory markers in the heart. Splenectomy suppressed tumor growth in saline-treated mice and further enhanced the tumor-suppressive effect of DOX. While splenectomy exacerbated DOX-induced reduction in cardiac output, it mitigated DOX-induced upregulation of cardiotoxicity and inflammatory markers in the heart.

Conclusion: The spleen plays critical roles in modulating both the cardiotoxic and tumor-suppressive effects of DOX. While splenectomy enhances the tumor-suppressive effect of DOX, its impact on DOX-induced cardiotoxicity is more complex as it exacerbates the reduction in cardiac output but ameliorates DOX-induced markers of cardiotoxicity and inflammation.