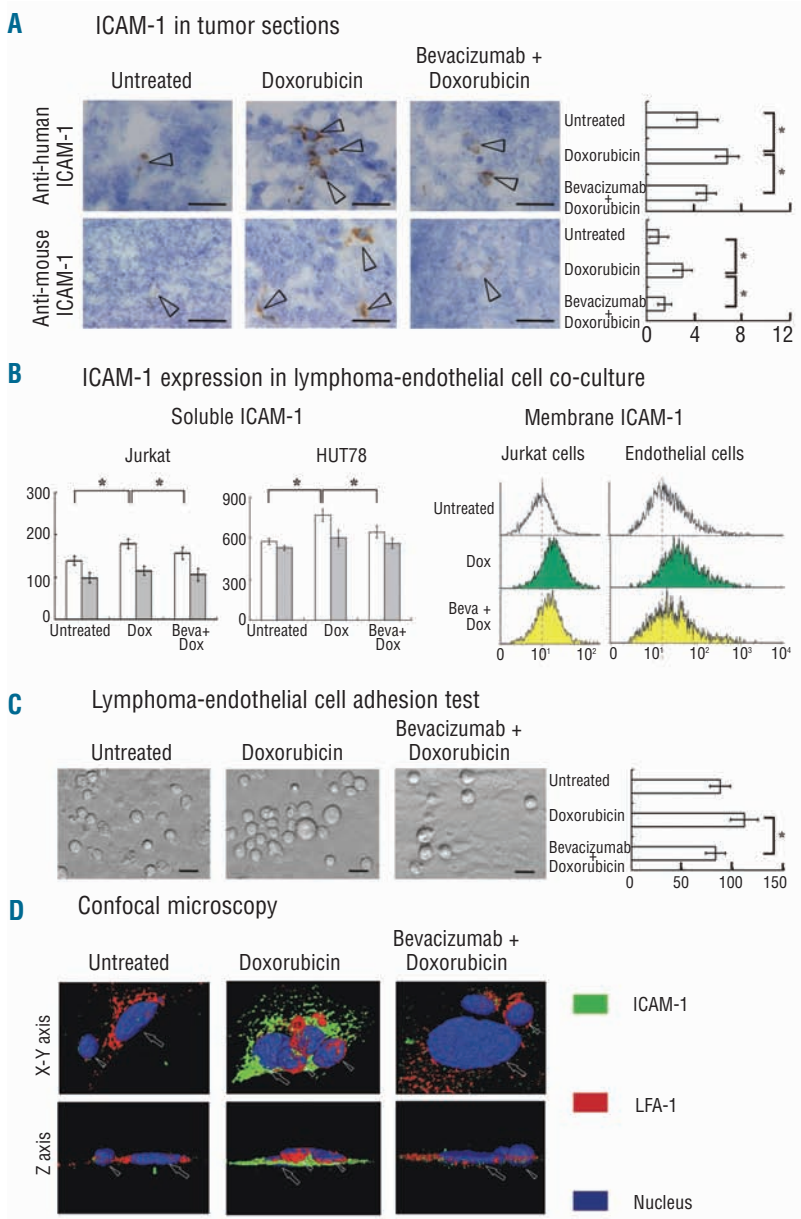


Bevacizumab potentiates chemotherapeutic effect on T-leukemia/lymphoma cells by direct action on tumor endothelial cells

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Online Supplementary Figure S1. Bevacizumab interrupted tumor-endothelial cell interaction through ICAM-1 downregulation. **(A)** *In vivo*, an immunohistochemical study using anti-human and anti-mouse ICAM-1 antibodies showed that doxorubicin induced ICAM-1 expression on tumor cells and on mouse endothelial cells. Addition of bevacizumab decreased doxorubicin-induced ICAM-1 expression, bar=20 μ m, * P <0.05. **(B)** *In vitro*, soluble ICAM-1 (left panel) and membrane ICAM-1 (right panel) were detected in cell culture by ELISA and flow cytometry, respectively. Left panel: when co-cultured in the same vial, combined bevacizumab and doxorubicin significantly inhibited doxorubicin-induced ICAM-1 expression. This was not observed in the co-culture system with 1 μ m pore millicell filter, which prevented direct contact between tumor and endothelial cells. \square Co-culture in the same vial. \blacksquare Co-culture with 1 μ m pore millicell filter, * P <0.05. Right panel: when co-cultured in the same vial, the doxorubicin-induced ICAM-1 was also inhibited by bevacizumab treatment. **(C)** Lymphoma-endothelial cell adhesion tests showed that cell adhesion was significantly decreased with bevacizumab and doxorubicin, when compared with doxorubicin alone. * P <0.05 bar=20 μ m. **(D)** On confocal microscope, doxorubicin induced close association of endothelial (arrows) and tumor cells (arrowheads), and strong ICAM-1/LFA-1 expression on endothelial cells, especially in areas where endothelial and tumor cells were in close contact. Addition of bevacizumab abrogated ICAM-1 expression by endothelial cells, and their close association with tumor cells.