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Ectopic expression of Vascular Cell Adhesion Molecule-1 (VCAM-1) by tumor cells interferes with CD8⁺ T cell effector functions and leads to tumor escape from immune attack

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Tumor escape from antigen-specific immune response is an important cause for failure of the immune system to control tumor growth, but the mechanisms that contribute to the emergence of resistant variants during immunotherapy remain poorly understood. Here, we describe a novel approach for identifying genes used by tumors to resist immune attack. Through multiple rounds of *in vivo* immune selection, we derived a highly resistant cell line (P3) from a susceptible cell line (TC-1/P0). Microarray analysis of the susceptible cell line (P0) and its resistant variant (P3) revealed vascular cell adhesion molecule-1 (VCAM-1) as one of the genes differentially up-regulated in P3. Retroviral transfer of VCAM-1 into P0 significantly increases the resistance of P0 against a vaccine-induced immune response. Both *in vitro* and *in vivo* studies show that expression of VCAM-1 by P0 tumor cells interferes with the release of cytotoxic granules and interferon- γ by effector CD8⁺ T cells. Further studies using mutated VCAM-1 show that this VCAM-1-induced impairment in T cell effector functions is mediated by its integrin receptor. These data provide evidence that ectopic expression of VCAM-1 in tumor cells can contribute to tumor escape from immune attack, and demonstrate that microarray analysis of resistant variants generated from *in vivo* immune selection represents a powerful approach for identifying novel immune escape mechanisms.