Necrotic tumor cell death in vivo impairs tumor-specific immune responses.

The manner in which cells die is believed to have a major impact on the nature of immune responses to their released Ags. In this study, we present the first direct analysis of tumor-specific immune responses to in vivo occurring tumor cell death through apoptosis or necrosis. Mice bearing thymidine kinase-transfected tumors were treated either with ganciclovir to induce tumor cell apoptosis in vivo or a vascular targeting agent, ZD6126, to induce tumor cell necrosis in vivo. In contrast to tumor apoptosis, induction of necrosis reduced the frequency and impaired the function of tumor-specific CD8(+) T cells. Adoptive transfer of lymphocytes from mice with apoptotic tumors into tumor-challenged mice resulted in a significant tumor protection, which was absent when splenocytes were transferred from mice with necrotic tumors. Anti-CD40 treatment reversed impaired Ag-specific CD8(+) T cell responses in these mice. These observations have not only fundamental importance for the development of immunotherapy protocols but also help to understand the underlying mechanism of in vivo immune responses to tumor cell death.