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Rapid functional exhaustion and deletion of cytotoxic T lymphocytes following immunization with recombinant adenovirus

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Replication-deficient adenoviruses (rec-AdV) expressing different transgenes are widely employed vectors for gene therapy and vaccination. We examined here the generation of β-galactosidase (βgal)-specific CTL following administration of βgal-recombinant adenovirus (Ad-LacZ). Using MHC class I tetramers to track βgal-specific CTL in different organs, we found that a significant expansion of βgal-specific CTL could only be achieved in a very narrow dose range ($2 \times 10^8 - 2 \times 10^9$ pfu). Functional analysis revealed that adenovirus-induced βgal-specific CTL produced only very low amounts of effector cytokines and were unable to lyse βgal peptide-pulsed target cells. Injection of optimal doses of Ad-LacZ into transgenic mice which express βgal exclusively in non-lymphoid organs, led to physical deletion of βgal-specific CTL. Our results indicate first that CTL deletion in the course of adenoviral vaccination is preceded by their functional impairment and second, that the outcome of rec-AdV vaccination depends critically on the antigen load in peripheral tissues. The presented findings thus impinge on the rationale to use adenoviral vectors in clinical vaccination.