Virus and Autoantigen-Specific CD4+ T Cells Are Key Effectors in a SCID Mouse Model of EBV-Associated Post-Transplant Lymphoproliferative Disorders.
Linnerbauer S, Behrends U, Adhikary D, Witter K, Bornkamm GW. PLoS Pathog. May 2014; 10: e1004068.

Long-term immunosuppression after transplantation dramatically increases the risk of malignancy, resulting in significant morbidity and death. There is a particular increase in the risk of non-melanoma skin cancer and virally-driven tumours. Post-transplant lymphoproliferative disorder (PTLD) occurs in up to 10% of patients, and in the majority of cases is secondary to EBV-infected B lymphocytes. (1) EBV infection persists lifelong in B cells but remains latent in immunocompetent hosts, contained by T cell surveillance. EBV-positive PTLD may be treated by infusion with EBV-specific T cells. (2) These therapeutic T cells are produced by stimulation of both CD4+ and CD8+ T cells with autologous EBV-infected B cells in vitro. There is some evidence to suggest that a broad T cell repertoire is more effective, as is a higher CD4+ to CD8+ T cell ratio. The CD4+ T cell response appears to be broadly distributed, with cells specific for both viral antigens and cellular antigens, although the importance of these different specificities to the response is not clear. In the study from Linnerbauer and colleagues, the efficacy of single virus-specific CD4+ T cells clones was investigated in a mouse model of PTLD. T cells which were specific for a virion antigen of EBV were effective at prolonging mouse survival, while other virus-specific clones had no beneficial effect. Interestingly, the key antitumoral CD4+ T cells were those which were specific for non-viral antigens. These antigens appeared to be restricted to transformed B cell lines and are potentially autoantigens, although they still require accurate identification. These data raise the possibility that T cells which are reactive against these autoantigens may also control EBV-negative B cell malignancies. Their precise definition may therefore facilitate the development of effective T cell therapies for PTLD.

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Tolerance Induction in Memory CD4+ T Cells Requires Two Rounds of Antigen-specific Activation.
David A, Crawford F, Garside P, Kappler JW, Marrack P, MacLeod M. Proc Natl Acad Sci U S A. May 12, 2014.

CD4+ T cells are central to the alloresponse against transplanted organs. (1) Controlling this response is key to improving outcomes after transplantation. CD4+ T cell memory responses are particularly detrimental and difficult to tolerate. (2,3) These responses are rapid and effective, which is due to the reduced requirement for co-stimulation and the high sensitivity to antigen of memory cells. Memory responses in transplantation may occur due to prior sensitization, heterologous immunity or cross-reactivity. The processes involved in tolerizing naïve CD4+ T cells have been well characterized, however it is not clear if and how tolerance may be induced in CD4+ memory T cells. Stimulation of naïve T cells with antigen in the absence of co-stimulation, for example with a soluble antigen or with co-stimulatory blockade, may promote tolerance. However, memory cells are primarily less dependent on a costimulatory signal. In the study from David and colleagues, the effects of soluble antigen on memory T cells were investigated in vivo. Fluorescent MHC Class II tetramers were used to track antigen-specific T cells in pre-immunized mice. Responses of tetramer-positive cells were assessed after stimulation with soluble antigen with or without adjuvant. As expected, memory CD4+ T cells exposed to soluble antigen proliferated and upregulated activation markers regardless of the presence of adjuvant. However, cells which were exposed to antigen in the absence of adjuvant failed to induce a functional response in the form of a delayed-type hypersensitivity response. More importantly, after a second challenge with the soluble antigen, tetramerpositive memory T cells were deleted. These data reveal a previously unrecognized method for promoting tolerance in memory CD4+ T cells. Given the importance of controlling the memory response in transplantation, harnessing this mechanism will be critical to the development of tolerogenic therapies.

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DOI: 10.1097/TP.0000000000000342