

A radio-resistant cell in the lymph node mediates deletional tolerance of CD8 T cells for a skin antigen expressed in melanocytes and melanoma

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Immunological tolerance toward tumor-associated antigens expressed on normal host tissues can limit the ability to elicit effective anti-tumor immune responses. However, depigmentation in tumor patients with immune responses against melanoma demonstrates that tolerance is limited for these proteins. Consistent with this, we previously demonstrated that, compared to Tyr^{-/-} animals, mice expressing the melanocyte differentiation protein tyrosinase (Tyr) have a decreased, but not absent, CD8⁺ T cell response to a Tyr-derived epitope. We have now produced TCR transgenic mice to examine the mechanisms contributing to tolerance towards this endogenously expressed, tissue-specific epitope. TCR transgenic mice have a decreased number of tyrosinase-specific CD8 T cells in the periphery relative to Tyr^{-/-} mice. Strikingly, though tyrosinase transcripts have been reported in thymic epithelial cells, there were no differences in thymic selection of tyrosinase-specific CD8 T cells in Tyr⁺ versus Tyr^{-/-} animals. Furthermore, transplant of Tyr⁺ thymi into Tyr^{-/-} mice did not diminish the magnitude of anti-Tyr CTL responses. Together, these results suggest that tolerance is not due to central deletion. In contrast, when CFSE-labeled TCR transgenic T cells were adoptively transferred into Tyr^{-/-} recipients, the cells divided but did not accumulate and underwent apoptosis. Thus, self-tolerance to Tyr is based on peripheral deletion. We utilized bone marrow chimeras to identify the cell type responsible for antigen presentation. Surprisingly, in Tyr⁺ animals lacking the restricting MHC molecule, the introduction of bone marrow expressing this molecule did not rescue steady-state presentation of endogenous tyrosinase. In the reciprocal chimeras, the elimination of radiosensitive cells expressing the restricting element did not diminish activation of adoptively transferred Tyr-specific T cells. Therefore, in contrast to other models, radio-resistant cells are responsible for this tolerogenic presentation. In vivo anti-CD62L blockade, followed by adoptive transfer, showed that this occurred only within the lymph node and eliminated the skin as a site of steady-state presentation. Analysis of surface phenotype of BM chimera lymphoid compartments revealed a radio-resistant CD11c⁺ cell within the skin-draining LN, consistent with the phenotype of Langerhans cells, suggested they may be responsible for this tolerogenic presentation. Overall, our results demonstrate that Tyr-specific T cells are tolerized by peripheral, but not central deletion and that a radio-resistant cell within the draining lymph node mediates tolerogenic presentation of this skin-associated antigen.