Targeting antigen to DC permits therapeutic termination of memory CD8+ T-cell responses by HSC-mediated gene therapy under immune-preserving conditions

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Abstract Established memory T-cell responses represent a key hurdle to protein and tissue replacement therapies as well as the application of tolerogenic immunotherapies in general. Development of appropriate therapies to effectively terminate deleterious memory T-cell responses would provide substantial therapeutic benefit. Autologous hematopoietic stem cell transplantation (HSCT) approaches has shown efficacy in severe autoimmune disease but recent work suggests including gene therapeutic approaches that engender antigen-specific tolerance would eliminate the need for the complete immune ablation that is the rationale for this therapy as currently applied. We have previously shown that genetic targeting of antigens to DC and other APC inactivates memory CD4+ and CD8+ T cells. Here we combine the approaches of targeted antigen expression and HSCT, but under immune preserving conditions, to show antigen-specific, therapeutic termination of memory CD8+ T-cell responses. A challenge for transplantation of antigen-encoding BM/HSC is immune-mediated rejection of the transplanted BM. We show that under the immune preserving conditions trialled, restricting antigen expression to differentiated DC using a CD11c promoter, by preventing immune attack of engrafting HSC allows effective engraftment of gene-modified BM in primed mice or those carrying defined populations Ag-specific CD8+ memory T cells. Furthermore, DC develop normally and present Ag for an extended period post-BMT, generating a long-term tolerogenic environment. Importantly, pre-existing cognate memory CD8+ T-cell responses were antigen-specifically ablated by the BMT procedure and deletion is a major contributor to this outcome. Collectively, we demonstrate the clinical potential of genetically-engineered HSCT as an approach to terminating unwanted memory T-cell responses for therapeutic benefit. The findings also imply that addition of gene-therapeutic tolerance approaches to current HSCT procedures may provide substantial clinical benefit.

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