Depletion of syndecan-4+ T lymphocytes by saporin-conjugated DC-HIL alleviates T cell-mediated inflammatory disease

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mice developed strong ear swelling, whereas DC-HIL-SAP-injected mice exhibited markedly reduced ear swelling by 80%. IgG-SAP had no effect. Our DC-HIL-SAP concentration was optimal since 20 nM caused 50% suppression, whereas 80 nM produced 80% reduction (similar dose of IgG-SAP causing increased toxicity). Histologic examination of Ox-painted ear skin in DC-HIL-SAP-injected mice revealed less thick ears and fewer infiltrating leukocytes (Fig. 2). Injection of DC-HIL-SAP following Ox challenge also reduced CH response. The unresponsive state to Ox lasted for 3 weeks (Fig. 3), even as these same mice were able to mount effective CH response against another contact allergen 2,4,6-trinitrochlorobenzene (TNCB) (Fig. 4).

These results indicate that a single infusion of DC-HIL-SAP efficiently blocks elicitation of an established immune response that lasts for 3 weeks and is restricted to the antigen introduced at the time of treatment.

We also examined the ability of DC-HIL-SAP to deplete SD-4+ T cells in immunized mice. Two days after challenging sensitized mice treated with DC-HIL-SAP or controls, SD-4+ T cells in Ox-painted ear skin or in draining lymph nodes (DLN) were counted by immunofluorescent staining (Fig. 5A) or by flow cytometry (Fig. 5B), respectively. There were nonto-very few T cells in untreated skin, but many CD4+ and CD8+ T cells in Ox-painted skin, almost all of which were SD-4+ (Fig. 5A). Numbers of CD4+ and CD8+ T cells in skin of mice injected with IgG-SAP were similar to those of mice treated with PBS, whereas both were reduced markedly following DC-HIL-SAP infusion. In DLN, infusion of DC-HIL-SAP depleted by 40% CD4+ and CD8+ T cells. These results indicate that a single infusion of DC-HIL-SAP depletes SD-4+ T cells in the inflamed skin and DLN.

Our studies in mice indicate that SD-4 can be targeted using toxin-bearing DC-HIL to alleviate a cutaneous inflammatory response that may find applications in many human disease states. The targeted nature (SD-4+ T cells) of this treatment may hold special advantage with respect to safety.

References/Footnotes:
1. T cell expression profiles of these receptors overlap but are disparate; cytotoxic T Lymphocyte antigen-4 (expressed by almost all recently activated T cells), programmed cell death-1 (restricted to effector T cells), B and T lymphocyte attenuator and T cell immunoglobulin mucin 3 (expressed preferentially by Th1 cells). Moreover, sustained high-level of programmed cell death-1 expression is a marker for T cells undergoing exhaustion in chronic viral infections and in cancer.