Bee-keepers hold clues for T-cell tolerance

Allergen-specific immunotherapy, which involves the repeated administration of high doses of an allergen, is an effective treatment for reducing allergic responses to bee venom and other allergens. Similarly to allergic patients that receive allergen-specific immunotherapy, non-allergic beekeepers are exposed to high doses of bee venom throughout the 6 month period of the bee-keeping season, during which they show only mild responses to bee stings. But how does repeated allergen exposure lead to the induction of tolerance to the allergen *in vivo*? Now, Akdis and colleagues report on a multi-year study in which they examined allergen-specific T-cell responses in bee-keepers during and outside of the bee-keeping season.

In this study, bee-keepers developed cutaneous late-phase swelling responses to bee stings during the first week of the working season, but stings throughout the rest of the season caused significantly milder inflammation. This decrease in the immune response to bee stings correlated with a marked increase in the number of interleukin-10 (IL-10)-producing T cells and a decrease in the number of interferon- γ (IFN γ)- and IL-4-producing T cells in the peripheral blood. These data support previous findings that T regulatory type 1 (T_R1) cells, which characteristically produce high levels of IL-10, are associated with decreased allergic responses. Indeed, when T cells were sorted from the peripheral blood of bee-keepers on the basis of cytokine production, IL-10-producing T cells were found to suppress the allergen-specific proliferation of IFN γ - and IL-4-producing T cells. Clonal analysis suggested that allergen-specific IL-10-producing T cells differentiated from the IFN γ - and IL-4-producing effector T-cell subsets rather than from naive cells. In addition, peripheral T-cell responses returned to baseline within 2 months of the end of the bee-keeping season. So, repeated exposure to bee venom causes a transient expansion of a T_R1-cell population that suppresses the allergen-specific responses of effector T-cell subsets.

The authors also examined the mechanisms that were involved in the suppressive function of the allergen-induced T_R1 cells. *In vitro* assays showed that cytotoxic T-lymphocyte antigen 4, programmed cell death 1 and IL-10, but not transforming growth factor- β , were involved in the suppression of allergen-specific effector T-cell proliferation by the induced T_R1 cells. Interestingly, a role for histamine receptor 2 (HR2) was also observed; the binding of histamine to HR2 on IL-4-producing T cells correlated with the induction of IL-10 production and the inhibition of allergen-specific T-cell proliferation *in vitro*.

Collectively, these findings indicate that transiently expanded T_R1-cell populations are important for keeping allergen-specific effector T-cell responses in check, which helps to explain how skin exposure to high doses of allergen leads to a decreased immune response to subsequent allergen exposures. In addition, the data suggest that antigen persistence is a prerequisite for long-term tolerance, which might have implications for other settings in which the induction of tolerance is a therapeutic aim.

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