Prevention of tracheal high-dose tolerance induction by granulocyte-macrophage colony stimulating factor-dependent restoration of antigen-presenting cell function

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The intrusion of airborne allergens into airways elicits eosinophilic inflammation, as represented by bronchial asthma. It has been shown that excessive amounts of allergen in murine trachea lead to an unexpected evasion of deleterious eosinophilic inflammation by inducing T cell tolerance. In the present study, the mechanisms of tracheal high-dose tolerance are examined with regard to accessory cell functions and the effects of pro-inflammatory cytokines on tolerance. Antigen-induced tracheal eosinophilia was suppressed on instillation of high doses of antigen into the trachea, while concurrent instillation of granulocyte-macrophage colony stimulating factor (GM-CSF) with the antigen restored the diminished responses. The restoration of eosinophilic infiltration by GM-CSF occurred in parallel with an increase in interleukin (IL)-4 production by CD4+ T cells from the mediastinal lymph nodes. This was found to reflect the empowerment of antigen-presenting cells by GM-CSF, because the impaired ability of Ia+ cells from the tolerant mice to stimulate IL-4-producing T cells is restored by GM-CSF administration. The prevention of tolerance by up-regulating accessory cell functions is a feature unique to GM-CSF, because another pro-inflammatory cytokine, IL-1β, failed to empower antigen-presenting cells. Thus, besides the induction of transforming growth factor-β-secreting CD4+ T cells, high-dose tolerance in the trachea includes an impairment of the accessory cell functions that support IL-4 production from T cells, which was reversed by GM-CSF. This report is the first demonstration that GM-CSF breaks the T cell tolerance of IL-4-producing T helper cells.

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