tized with IgE in the absence of IgG reacted with 1000-fold lower doses of antigen. Epitope density was inversely correlated with threshold dose for inducing reactivity. Finally, by adding back increasing amounts of IgG to the passively IgE-sensitized animals, they showed that FcRIIb does inhibit IgE responses when IgG levels are low.

CONCLUSIONS. Antigen-specific IgG does block IgE-mediated reactions in vivo by both direct competition and signaling via the inhibitory IgG receptor, FcγRIib.

REVIEWER COMMENTS. This was the first in vivo demonstration of specific IgG's ability to block IgE-dependent reactions, which has been suggested for many years by the frequently observed rise in allergen-specific IgG titer during successful immunotherapy. There are potentially important large differences between the mouse model and IgG induction in the context of allergen immunotherapy, including the fact that IgG-dependent anaphylaxis is well established in mice but uncertain to even exist in humans. It is also unclear from the article how the ratio of IgG to IgE in this model compares to the ratio of IgG and IgE specific to a particular allergen in human patients. However, the authors carefully and elegantly demonstrated the capacity and mechanistic details of IgG blocking antibody in vivo and strongly support the concept of blocking IgG in the context of immunotherapy.

CD137-Mediated Immunotherapy for Allergic Asthma

PURPOSE OF THE STUDY. Allergen-specific CD4+ T-helper 2 (Th2) cells are thought to be at the center of asthma pathogenesis because of their ability to secrete cytokines such as interleukin 4 (IL-4), IL-5, and IL-13, which result in many of the features of allergic inflammation. CD4+ cells recognize the allergen-derived target presented with class II on antigen-presenting cells along with costimulatory signals. One recently described costimulatory molecule is CD137. Studies using murine disease models have shown that stimulation of CD137 on T cells can modulate the immune system in beneficial ways, such as promoting tumor regression and suppressing autoimmunity. The authors of this study investigated the effect of CD137 stimulation on a murine model of allergic asthma.

METHODS. Allergic airway inflammation was induced in BALB/cByJ mice in the well-established manner involving systemic immunization to ovalbumin with alum followed by repeated aerosolized ovalbumin exposure. Control, nonspecific, antibody-treated mice were compared with mice treated with a single dose of agonistic anti-CD137 antibody given either before ovalbumin sensitization or after establishment of airway inflammation. Immunologic responses to ovalbumin were measured by ovalbumin-induced proliferation, in vitro cytokine production, and ovalbumin-specific immunoglobulin E and G1 titers. Changes in frequency of lymphocyte populations (CD4+, CD8+, CD19+, and CD4+CD25+) were measured by flow cytometry of total splenocytes. Adoptive transfer experiments were also conducted with CD4+ cells into severe combined immunodeficiency animals after control or anti-CD137 treatment.

RESULTS. A single dose of anti-CD137 treatment was effective in prevention of ovalbumin-induced airway inflammation and in vitro recall responses to ovalbumin continued to show suppressed Th2 cytokine responses (IL-4, IL-5, IL-13) and elevated Th1 (interferon γ [IFN-γ]) even after chronic ovalbumin exposure. Anti-CD137 given as a single dose after establishment of airway inflammation induced significant reduction of inflammation, even when given at a time point associated with chronic inflammation (32 weeks). In vitro cytokine responses were modulated by anti-CD137 treatment, which resulted in lower levels of ovalbumin-induced Th2 cytokines and elevated levels of IFN-γ in both lung and spleen cells. Anti-CD137 treatment was also associated with an increase of CD8+ cells and a decrease of CD19+ cells. The anti-CD137 affect was not entirely accounted for by this increase in CD8+ or IFN-γ, because inhibition of either resulted in only a partial reversal of its effect. Consistent with this, adoptively transferred CD4+ cells from animals that had been treated with anti-CD137 induced lower levels of airway inflammation compared with control-treated CD4+ cells.

CONCLUSIONS. CD137 is a potentially important target molecule for the modulation of Th2 inflammation.

REVIEWER COMMENTS. Asthma morbidity continues to rise in the pediatric population. This was the first report of the potential importance of the CD137 costimulatory pathway in the pathogenesis of Th2-driven airway inflammation. CD137 activation has been shown to be associated with both promotion of Th1 and regulatory T-cell activity in various disease models, and clinical trials targeting this pathway are likely to come soon for tumor immunology. Much more study is required, but this may emerge as an important new target for suppressing allergic inflammation.
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