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Out of the Orphanage and into the Clinic — Therapeutic Targeting of GATA3

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In 1986, Mosmann et al. reported that T-cell lines can be divided into type 1 (Th1) and type 2 (Th2) on the basis of patterns of cytokine production.[1] This classification of T cells according to their products subsequently expanded to include Th9, Th17, Th22, regulatory T cells, and follicular helper T cells. During the decade that followed, discoveries in microarray-based genomics led to the emergence of a collection of "orphan" genes that encode transcription factors responsible for driving the differentiation of these T-cell subsets, including GATA3, T-bet, ROR-γt, FOXP3, and others.[2] Each subset drives distinct immune and inflammatory responses and mediates distinct diseases.[2,3]

Allergic diseases are characterized by the production of antigen-specific IgE antibodies, which subsequently bind to and sensitize cells bearing high-affinity IgE receptors such as mast cells and basophils. Once cells in the lower airways have been sensitized, reexposure to an allergen can lead to early-phase and late-phase asthmatic responses. Events occurring during the early asthmatic response include mast-cell activation and bronchoconstriction, and acute bronchoconstriction typically resolves in a matter of hours. In many persons with asthma, this early response is followed by a late response that is characterized by a gradual, sustained bronchoconstriction thought to be mediated by an influx of inflammatory cells (especially eosinophils, basophils, and lymphocytes) and their products, including cytokines, chemokines, and chemical mediators. This provocation model for the response to an inhaled allergen is frequently used to study the biologic features of allergic asthma in humans and to explore the efficacy of asthma therapies.[4]

Key to the production of IgE antibodies and allergic inflammation are several cytokines typically produced by Th2 cells, such as interleukins 4, 5, and 13. These cytokines have multiple actions that include directing B cells to produce IgE antibodies and orchestrating eosinophilic inflammation. Many human cells make these cytokines, but Th2 lymphocytes are a primary source. Th2-cell differentiation and activation require the transcription factor GATA3, which activates the transcription of the signature Th2 cytokines.[5] Although among T cells GATA3 expression is specific to Th2 cells, GATA3 expression is also found in other cell types involved in allergic inflammation, including mast cells, eosinophils, and type 2 innate lymphoid cells, where its function is less well understood. Since type 2 inflammation is frequently associated with asthma,[6] type 2 cytokines are the target of novel therapies

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currently in development for the treatment of asthma that involves eosinophilia and type 2 cytokines.[7]

A number of companies have developed drugs aimed at blocking type 2 responses. Some of these drugs, most of which are biologics, bind to the cytokines themselves (e.g., lebrikizumab binds to interleukin-13 and mepolizumab and reslizumab bind to interleukin-5). Others block the cell-surface receptors of these cytokines (e.g., benralizumab in the case of the interleukin-5 receptor and dupilumab in the case of the common α chain of the receptor for interleukin-4 and interleukin-13).

Rather than betting on which type 2 cytokines to target for the treatment of asthma, Krug et al.,[8] now reporting in the *Journal*, explore a novel approach in which GATA3 is targeted, thereby taking a broader molecular swing at preventing production of all type 2 cytokines. They do so with a specific cell-permeable construct called SB010, a so-called DNAzyme designed as a 34-base, single-stranded synthetic antisense DNA that specifically binds to and cleaves GATA3 messenger RNA (see Fig. S1 and S4 in the Supplementary Appendix of the article, available at NEJM.org). In a placebo-controlled, phase 2a trial, which is based on the provocation model for the response to inhaled allergen, the investigators show that once-daily inhalation of 10 mg of SB010 for 4 weeks in patients with mild allergic asthma with sputum eosinophilia attenuates both the early-phase and late-phase asthmatic responses.

The evaluation of biomarkers suggests that inhaled SB010 modestly reduced mast-cell activation and eosinophil numbers in the airway and interleukin-5 levels in serum, but the drug had no effect on levels of exhaled nitric oxide or bronchial hyperreactivity. The treatment had few side effects, and data in the Supplementary Appendix show partial cleavage of GATA3 when studied in human tissues and purified T cells in vitro. Perhaps the most convincing effect of the treatment was a clinically significant blockade of the early- and late-phase bronchoconstriction after an inhaled-allergen challenge; it will be of interest to learn whether more prolonged treatments will have more profound results. As is always the case, additional phase 2 and phase 3 studies with more traditional end points such as lung function or asthma exacerbations must follow to get a better sense of the effectiveness of this treatment for asthma.

It is important to ask where a drug like this might fit into the armamentarium now available to physicians who treat patients with asthma. Although the inhibition of both early- and late-phase bronchoconstriction and the reduction in levels of mast-cell and eosinophilic biomarkers provide encouraging, proof-of-concept signs that targeting GATA3 (and therefore blocking type 2 responses) can inhibit allergic-airway responses, questions remain. For instance, the extent of the physiological improvement in early asthmatic response is more limited than that achieved with some commonly used bronchodilators (e.g., β_2-adrenergic agonists or blockers of the cysteinyl leukotriene receptor cysLT1), and the extent of the inhibition of the late asthmatic response is less than is typically achieved with inhaled glucocorticoid therapy. Nonetheless, having a single drug that inhibits both phases is impressive and rare, and it is reminiscent of the effects of omalizumab[9] and an antibody that blocks thymic stromal lymphopoietin, a cytokine that also promotes type 2 responses.[10]

The accumulating evidence of success related to drugs that block type 2 cytokine responses should be encouraging to patients with severe uncontrolled asthma and to the physicians who treat this disease. Although the results of this study have been three decades in the making, one has the sense that we are on the cusp of a new era in which asthma driven by Th2 cytokines can finally be tamed.

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