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Commentary

Asthma translational medicine: Report card

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ABSTRACT

Over the last 30 years, scientific research into asthma has focused almost exclusively on one component of the disorder – airway inflammation – as being the key underlying feature. These studies have provided a remarkably detailed and comprehensive picture of the events following antigen challenge that lead to an influx of T cells and eosinophils in the airways. Indeed, in basic research, even the term "asthma" has become synonymous with a T helper 2 cell-mediated disorder. From this cascade of cellular activation processes and mediators that have been identified it has been possible to pinpoint critical junctures for therapeutic intervention, leading experimentalists to produce therapies that are very effective in decreasing airway inflammation in animal models. Many of these compounds have now completed early Phase 2 "proof-of-concept" clinical trials so the translational success of the basic research model can be evaluated. This commentary discusses clinical results from 39 compounds and biologics acting at 23 different targets, and while 6 of these drugs can be regarded as a qualified success, none benefit the bulk of asthma sufferers. Despite this disappointing rate of success, the same immune paradigm and basic research models, with a few embellishments to incorporate newly identified cells and mediators, continue to drive target identification and drug discovery efforts. It is time to re-evaluate the focus of these efforts.

1. Introduction

Asthma is a chronic respiratory disease characterized by recurring attacks of impaired breathing, of varying intensities. The definition of asthma has four cardinal components – variable airflow obstruction (bronchoconstriction), symptoms, airway inflammation, and airway hyper-responsiveness (AHR) [1]. Asthma affects over 8% of Americans and that number continues to rise. Despite its widespread prevalence, increasing severity and associated rising healthcare costs measured in billions of dollars, few new drugs representing novel modes of action have been introduced over the last 30 years [2]. Indeed the mainstays of treatment, in the form of inhaled corticosteroids, β2 adrenoceptor agonists and cholinergic antagonists, have a long history and were first used clinically more than 50 years ago [2]. None of these drugs prevent asthma, and, while most patients obtain some level of symptomatic relief, a significant proportion continues to suffer, and new therapies are required urgently. The goal of therapy is two-fold – to limit the current impairment or symptoms, and to reduce the risk for a severe attack (exacerbation) in the future [1]. Since even patients with mild asthma have evidence for inflammation of the large and small airways, and the severity of the inflammation often correlates with the severity of the disease, attention in the last 30 years has focused on the mechanisms of airway inflammation and its suppression as a means of identifying new therapeutics.

Despite the dearth of new medications, asthma research is alive and well. Type the search term "asthma" into PubMed and there are almost 100,000 articles since 1980 (99,817 at the time of writing). The pathway of events which follow antigen sensitization and challenge have been painstakingly mapped in exquisite detail, and critical sites of regulation of the process have been identified involving both the innate and adaptive immune systems. The cellular pathology, recognition receptors, co-stimulatory molecules, key transcription factors, cytokines, chemokines, adhesion

Abbreviations: ACQ, asthma control questionnaire; AHR, airway hyper-responsiveness; AP-1, activator protein 1; APC, antigen-presenting cell; AQLQ, asthma quality-of-life questionnaire; BALF, bronchoalveolar lavage fluid; CTLA-4, cytotoxic T lymphocyte-associated antigen 4; cysLT, cysteinyl leukotrienes; DC, dendritic cell; EAR, early airway response; FEV1, forced expiratory volume in 1 second; FLAP, 5-lipoxygenase activating protein; GM-CSF, granulocyte-macrophage colony-stimulating factor; ICAM-1, intercellular adhesion molecule 1; ICOS, inducible costimulator; ICS, inhaled corticosteroid; IFN, interferon; IgE, immunoglobulin E; IL, interleukin; LAR, late asthmatic response; LPS, lipopolysaccharide; LT, leukotriene; mAb, monoclonal antibody; Maf-1, musculoaponeurotic fibrosarcoma 1; MHC, major histocompatibility complex; mRNA, messenger ribonucleic acid; NF-IL-6, nuclear factor interleukin-6; NKT, natural killer T cell; PD-1, programmed death 1; PEFR, peak expiratory flow rate; PG, prostaglandin; SCID, severe combined immunodeficiency; STAT, signal transducer and activator of transcription factor; TCR, T cell receptor; TGFβ, transforming growth factor β; Th, T helper cell; TLR, toll-like receptor; TNF, tumor necrosis factor; Treg, regulatory T cell; TSLP, thymic stromal lymphopoietin; VCAM-1, vascular cell adhesion protein 1; VLA-4, very late antigen 4.

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molecules, and other mediators, have been investigated and incorporated into a comprehensive, detailed, unifying model of the events that translate into asthma. Such achievements seemed to hold great promise. As concluded in an article in *Nature Biotechnology* in 2000 [3] "Significant recent advances on all fronts suggest that significant new and better treatments are on their way." The start of the last decade seemed to hold much optimism and promise. What happened?

1.1. Purpose of this review

The goal of this article is to review the evidence for the research paradigm of asthma developed over the last 30 years as an immune response gone awry, and evaluate the clinical success of this model. Based on the mechanistic pathway that has emerged from research, a number of key targets have been identified and new therapeutics developed (Fig. 1). A significant number of these have now completed Phase 2 clinical trials in asthmatic subjects, such that the translational success of the mechanisms of airway inflammation can be evaluated. Not included in this commentary are studies with therapeutic agents that, while intended to target the inflammatory component of asthma, could also influence other features of the disorder thereby adding a degree of confusion to the interpretation of the results. These agents include iloprost, prostaglandin D2 antagonists, 5-lipoxygenase activating protein (FLAP) inhibitors, phosphodiesterase 4 inhibitors, and inhibitors of various kinases. This article focuses on agents that relate unambiguously to the immune paradigm defined by basic research and complemented by clinical observations in asthma patients.

As a number of clinical studies are ongoing, it is highly likely that new results will emerge in the period between writing this commentary and its publication, which could modify the conclusions reached. Indeed, let us hope that is the case since the clinical results obtained so far are disappointing.

2. Defining asthma pathophysiology: basic research studies

2.1. Introduction

Frequently, clinical asthma has been associated with atopy and elevated immunoglobulin E (IgE) levels, typifying an allergic component. However, murine "asthma" models do not show a distinct role for IgE in the pathogenesis of asthma. Bronchial inflammation and AHR occur to the same extent in $IgE^{-/-}$ and wild-type mice subjected to antigen challenge, while mast cell activation and mediator release in response to ovalbumin challenge are also observed in IgE deficient mice and those lacking the active IgE receptor, FcεRI (see [4]). While this might be due, in part, to a species-specific role for the IgG1 isotype, at a basic research level the term asthma has now become synonymous with a T helper 2 (Th2) cell-mediated disorder. According to this paradigm, allergic sensitization and subsequent challenge results

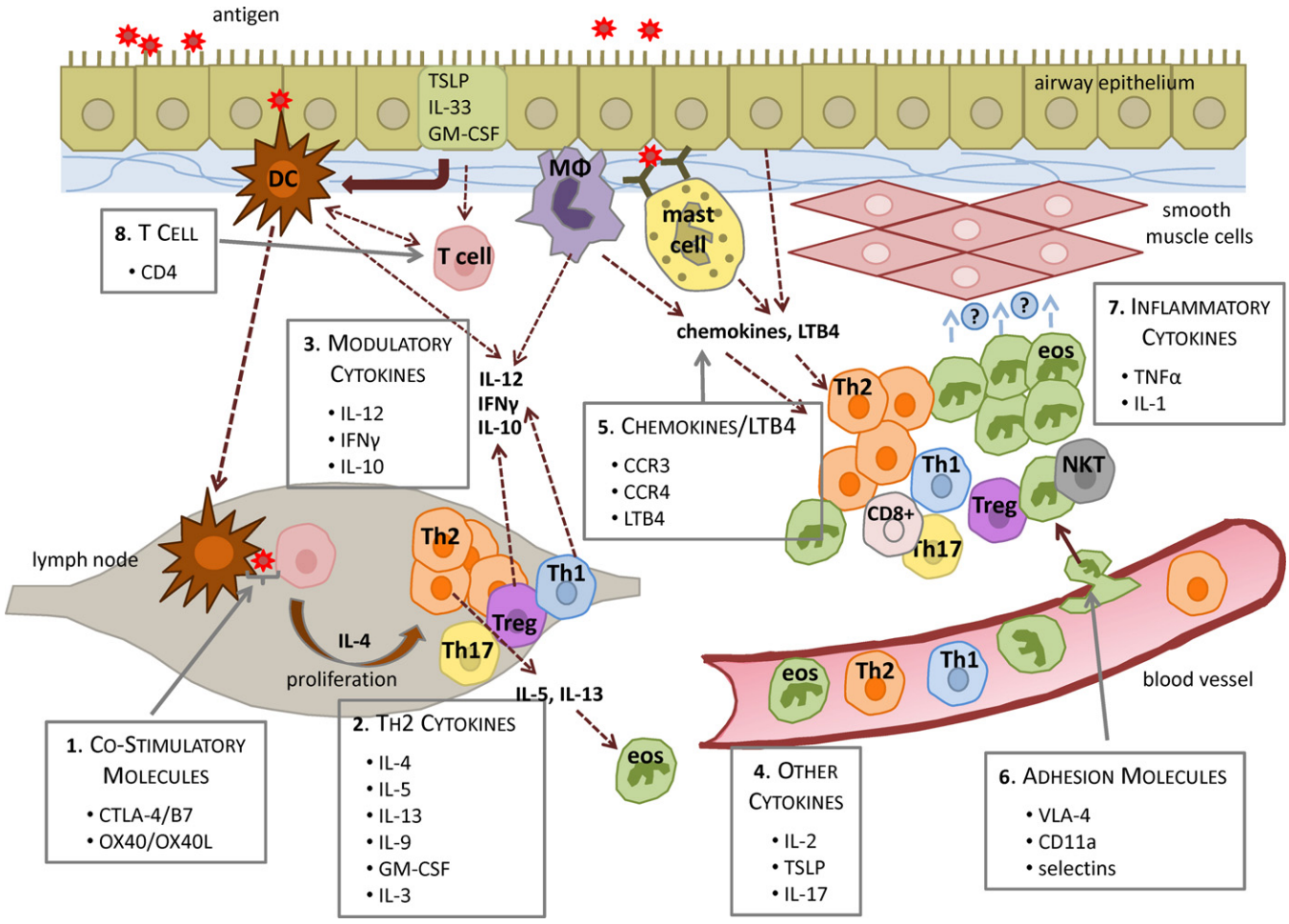

Fig. 1. Basic research has provided a detailed map of the events following antigen challenge that culminate in an asthma-like response in animal models. An abbreviated version is depicted, highlighting the components within this immune cascade that have targeted with novel therapeutics to treat the clinical condition (shown in the grey boxes). The numbers of each box relate to the sequence in which they are discussed in the text. DC, dendritic cell; Mϕ, macrophage; eos, eosinophil. Other abbreviations as defined in the text.