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Patient stratification and the unmet need in asthma

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ABSTRACT

Asthma is often described as an inflammatory disease of the lungs and in most patients symptomatic treatment with bronchodilators or inhaled corticosteroids is sufficient to control disease. Unfortunately there are a proportion of patients who fail to achieve control despite treatment with the best current treatment. These severe asthma patients have been considered a homogeneous group of patients that represent the unmet therapeutic need in asthma. Many novel therapies have been tested in *unselected asthma* patients and the effects have often been disappointing, particularly for the highly specific monoclonal antibody-based drugs such as anti-IL-13 and anti-IL-5. More recently, it has become clear that asthma is a syndrome with many different disease drivers. Clinical trials of anti-IL-13 and anti-IL-5 have focused on biomarker-defined patient groups and these trials have driven the clinical progression of these drugs. Work on asthma phenotyping indicates that there is a group of asthma patients where T helper cell type 2 (Th2) cytokines and inflammation predominate and these type 2 high (T2-high) patients can be defined by biomarkers and response to therapies targeting this type of immunity, including anti-IL-5 and anti-IL-13. However, there is still a subset of T2-low patients that do not respond to these new therapies. This T2-low group will represent the new unmet medical need now that the T2-high-targeting therapies have made it to the market. This review will examine the current thinking on patient stratification in asthma and the identification of the T2-high subset. It will also look at the T2-low patients and examine what may be the drivers of disease in these patients.

Contents

Abbreviations: ACOS, asthma and chronic obstructive pulmonary disease overlap syndrome; ACQ, Asthma Control Questionnaire; AHR, airway hyperresponsiveness; ASM, airway smooth muscle; BAL, bronchoalveolar lavage; BHR, bronchial hyperresponsiveness; CLCA1, chloride channel, calcium activated family member 1; COPD, chronic obstructive pulmonary disease; CRTh2, chemoattractant receptor-homologous molecule expressed on Th2 cells; cysLTs, cysteinyl leukotrienes; DCs, dendritic cells; DPP-4, dipeptidyl peptidase-4; FeNO, fractional exhaled nitric oxide; FEV1, Forced Expiratory Volume in 1 s; GINA, Global Initiative for Asthma; GM-CSF, granulocyte macrophage colony-stimulating factor; HRV, human rhinovirus; ICSs, inhaled corticosteroids; IFN, interferon; Ig, immunoglobulin; IL, interleukin; ILCs, innate lymphoid cells; LABA, long-acting beta-agonist; LTRA, leukotriene receptor antagonist; PEF, peak expiratory flow; PEFR, peak expiratory flow rate; PGD_2, prostaglandin D_2; POSTN, periostin, osteoblast specific factor; SARP, severe asthma research program; serpinB2, serine peptidase inhibitor, clade B, member2; STAT, signal transducer and activator of transcription factor; T2, type 2; Th2, T helper cell type 2; TLR, Toll-like receptor; TNF, tumor necrosis factor; TSLP, thymic stromal lymphopoietin.

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1. Introduction

According to the Global Initiative for Asthma (GINA), asthma is defined in the following way:

"Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation" (GINA, 2016).

This definition was changed in 2014 to include the statement that asthma is a heterogeneous disease. This change is in part driven by clinical experience from the monoclonal antibody trials for anti-interleukin (IL)-5, anti-IL-13 and anti-IL-4 receptor α (anti-IL-4Rα), which demonstrated that these highly specific therapies are generally more efficacious in groups of patients selected on the bases of target mechanism or pathway activation.

Classically, asthma was thought of as a T helper cell type 2 (Th2)-driven disease and this has driven the development of therapies targeting this biology. In this review, we will use the emerging terminology of type 2 (T2) asthma, taking into consideration that other cells, such as group 2 innate lymphoid cells (ILC2s) may contribute to the immune responses involved (Barnes, 2001; McKenzie, 2014; Fahy, 2015). Importantly, recent work indicates that asthma has both a T2-high and a T2-low phenotype (Woodruff et al., 2009). The underlying biology and key pathological drivers in the T2-low patients are poorly understood meaning that there are few therapies being developed to treat these patients (Moore et al., 2010). This review will discuss current thinking on the pathology of asthma and the methods used to define stratified groups of patients. In addition, it will make the case for more work to understand the T2-low asthma group and define where the unmet medical need is likely to lie in light of the imminent approval of therapies targeting T2-high-associated pathways.

1.1. The molecular pathology of T Helper 2 cytokine high (T2-high) asthma

T2-high asthma is associated with allergic inflammation despite the fact that some eosinophilic patients with late-onset disease may be less allergic (Robinson et al., 1992; Peters, 2014). Allergens or other harmless stimuli activate the airway epithelium to release cytokines such as thymic stromal lymphopoietin (TSLP), IL-33 and IL-25 (Hammad & Lambrecht, 2015). Activation of the epithelium may occur through activation of protease activated receptor 2 (PAR2) by allergen-associated protease activity or the release of proteases from mast cells (Boitano et al., 2011). Tissue damage appears to be the key to production of IL-33 which is released by necrotic cells and acts as an alarmin (Luthi et al., 2009). There is evidence that TSLP is induced by oxidative stress and inflammatory cytokines such as tumor necrosis factor (TNF)-α and IL-1β (Lee & Ziegler, 2007; Nakamura et al., 2008). TSLP, IL-33 and IL-25 drive the activation of a T2-immune response to allergens. In the theory of T cell-mediated responses, allergens are taken up by dendritic cells (DCs) that then migrate to the draining lymph nodes. TSLP causes the maturation of DCs that upregulate major histocompatibility (MHC) class II and OX40L and interact with naïve T cells in the draining lymph node (Liu, 2006; Wang & Liu, 2007). TSLP-activated DCs drive the differentiation of naïve T cells to inflammatory Th2 cells that produce high levels of IL-5, IL-13 and TNF-α but low levels of IL-10 (Soumelis et al., 2002; Liu, 2006). These T cells migrate back to the airways where they drive a T2-mediated inflammatory response. This model explains the activation of allergic inflammation by the adaptive immune system. However, mice lacking T and B cells will still develop eosinophilic airway inflammation to innocuous stimuli (Hammad & Lambrecht, 2015), indicating that there is an innate activation of T2 immunity. The characterization of innate lymphoid cells (ILCs) demonstrated how T2 responses could develop in the absence of Th2 cells (Hammad & Lambrecht, 2015). Broadly speaking, ILCs can be classed as ILC1, ILC2 or ILC3 depending on the cytokines that they produce (Spits et al., 2013) and transcription factor expression. ILC1s characteristically express the T-bet transcription factor and produce interferon (IFN)-γ and TNF-α; ILC2s express the GATA3 transcription factor and produce the classical T2 cytokines IL-4, IL-5 and IL-13, whereas ILC3s express RORγt and produce IL-17A, IL-22 and granulocyte macrophage colony-stimulating factor (GM-CSF) (Spits et al., 2013; Artis & Spits, 2015). The biology of ILCs is still emerging and there may be many subtypes that fall between these groups. There is also literature to suggest that ILC phenotypes display a degree of plasticity, for example, IFN-γ producing ILC1 and IL-17 producing ILC3s can switch between these phenotypes depending on the cytokines in the environment (Vonarbourg et al., 2010; Bernink et al., 2013; Artis & Spits, 2015; Bernink et al., 2015). A full review of ILC biology is outside the scope of this review but there are a number of recent reviews on these cells (Artis & Spits, 2015; Sonnenberg & Artis, 2015). In the context of asthma, there has been considerable focus on the role of ILC2s since they are capable of producing the classical T2 cytokines that drive eosinophilic airway disease. ILC2s are activated and modulated by many of the epithelial-derived cytokines that are involved in the maturation of DCs in T2 responses including TSLP, IL-33 and IL-25 (Imai et al., 2013; Kim et al., 2013; Salimi et al., 2013; Artis & Spits, 2015). It is speculated that ILC2s may provide a first line of innate defense against infection of the airways prior to the induction of an adaptive immune response (Licona-Limon et al., 2013). Recently, it was demonstrated in vitro that virally induced IL-33 release from the bronchial epithelium may activate ILC2s and drive the production of T2 cytokines (Jackson et al., 2014). This provides a direct link between viral infection and T2 responses.

The link between Th2-mediated inflammation and asthma pathology is well founded and has now been clinically proven by the successful trials of therapies that target aspects of Th2 biology, including anti-IL-4Rα, anti-IL-13 (Barnes, 2008; Corren, 2013b; Wenzel et al., 2013) anti-IL-5 (Robinson et al., 1992; Sanderson, 1992; Corrigan et al., 1993; Carroll et al., 1996; Giembycz & Lindsay, 1999; Rothenberg & Hogan, 2006; Kouro & Takatsu, 2009), anti-immunoglobulin (Ig) E (Burrows et al., 1989; Sunyer et al., 1995; Hamelmann, 2007) and initial studies with anti-TSLP (Gauvreau et al., 2014b). However, to the surprise of many in the field of respiratory research, the initial results of anti-IL-13 and anti-IL-5 trials were disappointing. What changed the prospects for these drugs was the use of pre-selection of patients for clinical trials based on biomarkers that indicated active T2-mediated inflammation. The implications of this work are that there is a group of patients whose asthma is driven by T2 immunity and that there are severe asthma patients whose disease is independent of T2 immunity or low T2. These studies provide definitive clinical evidence that asthma is a heterogenic disease. Considerable work has been performed to understand the different groups, phenotypes or endotypes of asthma patients and to define methods to identify patients in the clinic. This work is of vital importance to ensure that therapies are targeted to the appropriate patient groups.

2. Phenotyping asthma

2.1. Defining asthma: endotypes and phenotypes

The heterogeneous nature of asthma creates a problem for the development of therapies targeting specific disease mechanisms that may only be present in some patients; how do we identify the patients that are more likely to respond to a specific therapy? The process of classifying patients into different categories is often referred to as phenotyping. Phenotyping can be made at different levels from clinical manifestations, inflammatory cell counts in tissue and blood and down to molecular patterns in tissue and serum. However, it is not always clear how a specific phenotype may relate to the mechanisms that drive disease and recent literature highlights the need to define patients based on mechanistic endotypes (Anderson, 2008; Lotvall et al., 2011;