Immunobiology xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Immunobiology

journal homepage: www.elsevier.com/locate/imbio

Review

Mode of dendritic cell activation: The decisive hand in Th2/Th17 cell differentiation. Implications in asthma severity?

Heleen Vroman, Bernt van den Blink, Mirjam Kool*

Department of Pulmonary Medicine, Erasmus MC, Rotterdam, The Netherlands

ARTICLE INFO

Article history:
Received 16 May 2014
Received in revised form 12 August 2014
Accepted 5 September 2014
Available online xxx

Keywords:
Asthma
Dendritic cells
T helper 2 cells
T helper 17 cells
Eosinophils
Neutrophils

ABSTRACT

Asthma is a heterogeneous chronic inflammatory disease of the airways, with reversible airflow limitations and airway remodeling. The classification of asthma phenotypes was initially based on different combinations of clinical symptoms, but they are now unfolding to link biology to phenotype. As such, patients can suffer from a predominant eosinophilic, neutrophilic or even mixed eosinophilic/neutrophilic inflammatory response. In adult asthma patients, eosinophilic inflammation is usually seen in mild-to-moderate disease and neutrophilic inflammation in more severe disease. The underlying T cell response is predominated by T helper (Th) 2, Th17, or a mixed Th2/Th17 cell immune response. Dendritic cells (DCs) are "professional" antigen presenting cells (APCs), since their principal function is to present antigens and induce a primary immune response in resting naive T cells. DCs also drive the differentiation into distinctive Th subsets. The expression of co-stimulatory molecules and cytokines by DCs and surrounding cells determines the outcome of Th cell differentiation. The nature of DC activation will determine the expression of specific co-stimulatory molecules and cytokines, specifically needed for induction of the different Th cell programs. Thus DC activation is crucial for the subsequent effector Th immune responses. In this review, we will discuss underlying mechanisms that initiate DC activation in favor of Th2 differentiation versus Th1/Th17 and Th17 differentiation in the development of mild versus moderate to severe asthma.

Contents

Abbreviations: Ag, antigen; AHR, airway hyper responsiveness; APC, antigen presenting cell; ATS, American Thoracic Society; BAL, bronchoalveolar lavage; Bcl-6, B-cell lymphoma; C, complement; cDC, conventional DC; CLR, C-type lectin receptor; DAMP, damage associated molecular pattern; DC, dendritic cell; DC-SIGN, DC-specific intracellular adhesion molecule 3-grabbing non-integrin; DEP, diesel exhaust particle; Foxp3, forkhead box protein 3; GATA-3, GATA-binding protein 3; GINA, Global Initiative for Asthma; GM-CSF, granulocyte–macrophage colony-stimulating factor; HDM, house dust mite; GWAS, genome wide association studies; ILC, innate lymphoid cell; IRF, interferon regulatory factor; LPS, lipopolysaccharide; MD2, myeloid differentiation 2; MLN, mediastinal lymph node; MR, mannose receptor; NLR, nucleotide oligomerization domain like receptors; NOD, nucleotide oligomerization domain; PAMP, pathogen associated molecular pattern; pDC, plasmacytoid DC; PPR, pathogen recognition receptor; RIG, retinoic acid-inducible gene; RLR, retinoic acid-inducible gene-I-like receptors; RORγt, retinoid orphan receptor γt; SAA, serum amyloid A; SNP, single nucleotide polymorphism; STAT, signal transducer and activator of transcription; T-bet, T-box transcription factor; TCR, T cell receptor; Tfh, follicular T cell; Th, T helper; TLR, Toll-like receptor; TNFAIP3, tumor necrosis factor alpha interacting protein 3; TNIP, TNFAIP3 interacting protein; Treg, regulatory T cell; TSLP, thymic stromal lymphopoietin.

* Corresponding author at: Department of Pulmonary Medicine, Erasmus University Medical Center, Dr. Molewaterplein 50, 3015 GE Rotterdam, The Netherlands. Tel.: +31 10 7048526.
E-mail address: m.kool@erasmusmc.nl (M. Kool).

http://dx.doi.org/10.1016/j.imbio.2014.09.016
0171-2985/

Introduction

Asthma is a heterogeneous chronic inflammatory disease of the airways, which is initiated by exposure to environmental factors (Wenzel 2012). Phenotypically, asthma can be classified as mild, moderate or severe according to National Asthma Education and Prevention Program, Global Initiative for Asthma (GINA), or American Thoracic Society (ATS) guidelines (Bousquet 2000; Brusselle and Kraft 2014). Mild to moderate asthma is initiated by an allergic response to allergens and often referred to as allergic asthma. It is defined by airway hyper responsiveness (AHR) of the bronchioles to a specific stimuli, increased mucus production and airway remodeling. T helper (Th) 2 cells initiate allergic immune responses in mild to moderate asthma. Th2 cytokines are produced by both Th2 cells (IL-4, IL-5, and IL-13) and type 2 innate lymphoid cells (ILCs) (IL-5 and IL-13). These cytokines facilitate the classical allergic responses, such as IgE class switching by B cells (IL-4), eosinophilic infiltration (IL-5), and goblet cell hyperplasia (IL-13) (Holgate 2012; Li and Hendriks 2013). In contrast, severe asthmatic patients display an aggravated asthmatic phenotype, with severe and increased number of exacerbations and patients are less responsive to corticosteroid treatment (Wenzel et al. 1997). Severe asthma patients are often non-allergic, but display asthmatic symptoms in response to other stimuli such as diesel exhaust particles (DEP), viruses, and cigarette smoke (Thomson et al. 2004; Ghio et al. 2012). Inflammation in severe asthma patients is generally defined by a neutrophilic or mixed eosinophilic/neutrophilic infiltration. The neutrophilic influx is thought to be mediated by Th17 cells, however Th1 cells are also associated with severe asthma. Moderate and severe asthma patients display elevated levels of IL-17A in both bronchoalveolar lavage (BAL) fluid and lung biopsies (Molet et al. 2001; Chakir et al. 2003). Th17 cytokines mediate an increased infiltration of neutrophils by activating the epithelium to secrete the neutrophil chemo-attractant CXCL8 (Newcomb and Peebles 2013). Additionally, Th17 cytokines will mediate increased mucus production (IL-17) and severe airway remodeling (IL-17/IL-22) leading to recurrent exacerbations (Aujla and Alcorn 2011). Dendritic cells (DCs) are potent antigen presenting cells (APCs), which are essential for inducing and priming of proper Th responses (Hammad and Lambrecht 2008; Kool et al. 2011). DCs are crucial for both the initiation as well as the maintenance of the inflammatory asthmatic response (Lambrecht et al. 2000; van Rijt et al. 2005). In this review we will discuss a potential role for DC activation as initiator for Th2, Th1 or Th17-driven asthma.

Immunology of house dust mite driven asthma

Sensitization to house dust mite is pivotal for the development of most acute childhood asthma, since up to 85% of patients with recurrent asthma are allergic to HDM during hospitalization (Nelson et al. 1996; Gregory and Lloyd 2011). HDM contains at least 22 different allergen groups, recently reviewed by Jacquet (2013). Besides HDM allergens, microbial pattern associated molecular patterns (PAMPs) such as lipopolysaccharide (LPS), chitin and β-glucans are frequently found in mite excretes. Several allergen groups within HDM, like Derp1 and Derp3 display protease activity which can damage the airway epithelial layer and allow entrance to the lungs (Jacquet 2013). Airway DCs are exposed to HDM, take up the allergen, become activated, and undergo maturation. During activation, CCR7 will be upregulated, necessary for DC migration toward the draining mediastinal lymph node (MLN) (Förster et al. 1999). In the MLN, fully matured DCs activate naïve T cells to proliferate and differentiate into effector T helper cells (Lambrecht and Hammad 2012) (Fig. 1).

Lung DC subsets

Lungs can be divided into the large conducting airways and the interstitium containing alveolar septa and capillaries. It has become clear that at least four $CD11c^+MHCII^+$ DC subsets can be found in the lungs of mice. During steady state, three different DC subsets can be found. These three DC subsets contain conventional DCs (cDCs), consisting of 2 subsets: $CD103^+$ cDCs and $CD11b^+$ cDCs, and plasmacytoid DCs (pDCs) (Plantinga et al. 2010). The $CD103^+$Langerin$^+$ cDCs underline the epithelium of the large conducting airways and have the potential to protrude their dendrites into the lumen of the airways in an active search for antigens. The $CD11b^+$ cDCs can be found in the lamina propria underneath the epithelium (Lambrecht and Hammad 2012). For optimal Th2 cell priming after HDM exposure, this $CD11b^+$ cDC subset is fundamental (Plantinga et al. 2013). During an inflammatory response a fourth DC subset arises in the lung, the inflammatory monocyte-derived DC (mo-DC), which will amplify the secondary local inflammatory response. This review focusses on the activation of lung DCs in general. The function of different DC subsets in the lung are reviewed in more detail by Lambrecht and Hammad (2012) and Plantinga et al. (2013).

House dust mite mediated recognition, uptake and activation of DCs

HDM can be recognized by specific pattern recognition receptors (PPRs) that are expressed by both immune cells as well by epithelial cells. PPRs can be subdivided into C-type lectin receptors (CLRs), Toll-like receptors (TLRs), nucleotide oligomerization domain (NOD)-like receptors (NLRs) and retinoic acid-inducible gene (RIG)-I-like receptors (RLRs) (Jacquet 2013; Wang 2013). PPRs recognize PAMPs as well as damage-associated molecular patterns (DAMPs). Beside containing several PAMPs, HDM can also lead to DAMP release in a TLR4 dependent manner by airway epithelial cells, such as heat shock proteins, ATP, and uric acid and enhance Th2 immunity (Idzko et al. 2007; Kool et al. 2011). For instance, uric acid is released after allergen exposure in mice and asthmatic patients and is critical for Th2 sensitization and the secondary inflammatory response (Kool et al. 2011).

HDM recognition and uptake by DCs are mediated through binding with specific CLRs. The mannose receptor (MR) mediates recognition and uptake of Derp1 (Charbonnier et al. 2002), whereas both Derp1 and Derp2 are recognized and taken up by DC-specific intracellular adhesion molecule 3-grabbing non-integrin (DC-SIGN) (Hsu et al. 2010; Emara et al. 2012; Salazar and Ghaemmaghami 2013). DCs of HDM-allergic patients show a higher MR expression and are more efficient in the uptake of HDM in comparison to DCs of non-allergic patients (Charbonnier et al. 2002). Allergen uptake by MR also promotes Th2 immunity, whereas

Please cite this article in press as: Vroman, H., et al., Mode of dendritic cell activation: The decisive hand in Th2/Th17 cell differentiation. Implications in asthma severity? Immunobiology (2014), http://dx.doi.org/10.1016/j.imbio.2014.09.016