European Journal of Pharmacology 808 (2017) 14–20

Contents lists available at ScienceDirect

European Journal of Pharmacology

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

Full Length Article

The role of endosomal toll-like receptors in asthma

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ARTICLE INFO

Keywords:
Asthma
Allergic inflammation
Atopy
Toll-like receptors
Hygiene hypothesis
Immunomodulation
Inflammation
Innate immunity

ABSTRACT

Asthma is a heterogeneous inflammatory disease caused by association of genetic and environmental factors and its incidence has significantly increased over the latest years. The clinical manifestations of asthma are the result of airway hyper-reactivity to a variety of triggers such as aeroallergens, viral and bacterial components. Toll-like receptors (TLRs) are pathogen associated molecular pattern receptors, which are also expressed in the lung tissue as well as in several cells of the innate and adaptive immune system. Ligation of TLRs results in alterations in the expression of several inflammatory and anti-inflammatory mediators, which are known to be involved in the pathogenesis of asthma. The endosomal TLRs have been shown to be associated with the induction of asthmatic inflammation (TLR3), and with disease exacerbations (TLR7, TLR8 and TLR9). Targeting these receptors seems to be an effective choice for suppressing airway inflammation, eosinophilia and airway hyperresponsiveness in asthmatic patients. In this review we provide information regarding endosomal TLRs and their role in the pathogenesis of asthma as well as their potential use as targets for the development of novel treatments for the therapy of asthma.

1. Introduction

Asthma is a heterogeneous inflammatory disease, characterised by a history of respiratory symptoms including wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity usually related to variable expiratory flow limitation (Global Initiative for Asthma, 2014). The disease is more common in industrialised and urbanised areas and its prevalence has increased worldwide over the last decades (Mannino et al., 2002; Masoli et al., 2004; James et al., 2010). It is estimated that asthma affects approximately 300 million people of all ages, races and geographic origins whereas it is believed that over 100 million more people will be affected by 2025 (Masoli et al., 2004).

The clinical manifestations of asthma are the result of airway hyper-reactivity to several stimuli. This hyper-reactivity is associated to inflammatory infiltration of the airways by neutrophils, monocytes and eosinophils, leading to excessive mucus production and hyperplasia of the airway smooth muscle, which result in airflow limitation (Busse and Lemanske, 2001).

It is now well established that the main immunological pathway in the development of allergic asthma includes infiltration and accumulation of polarised CD4 T helper 2 (Th2) cells in the airway mucosa (Kay, 2001). These cells, produce and secrete several inflammatory cytokines, such as interleukin (IL) 4, IL5, IL9, and IL13, which are related to the fundamental pathologic features of asthma (Robinson et al., 1992). In general, Th2 cells contribute to the pathology of allergic inflammation in asthma via two different mechanisms. The first includes IL4 production by the Th2 cells which stimulates B lymphocytes to produce allergen-specific immunoglobulin (Ig)E. IgE is subsequently bound to specific receptors (FcεR) expressed on cell surface of mast cells and this reaction leads to their degranulation resulting in the allergic response and airway hyperresponsiveness (Platts-Mills, 2001). The second mechanism through which Th2 cells result to airway hyperresponsiveness in asthmatic patients is by recruiting eosinophils to the airways mainly though production of IL5 (Platts-Mills, 2001). Following their recruitment, eosinophils produce and release several mediators which contribute to the development of airway hyperresponsiveness (Hogan et al., 1997).

It is widely supported that Th1 cytokines have the ability to downregulate Th2 responses (Mosmann and Coffman, 1989). Since Th2 cells and their mediators have principal role to the pathophysiology of allergic asthma it has been suggested that the enhanced number

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http://dx.doi.org/10.1016/j.ejphar.2016.09.033
Received 2 November 2015; Received in revised form 6 April 2016; Accepted 23 September 2016
Available online 24 September 2016

and function of these Th2 cells is related to a decreased activation of Th1 cells probably caused by environmental factors (Camateros et al., 2006). This is the basis of the so-called hygiene hypothesis, which suggests that a lack of exposure to infective microorganisms during childhood increases susceptibility to allergic diseases and asthma due to deficient maturation of the immune system (Strachan, 2000; Romagnani, 2007). This hypothesis has been based on the presence of evidence that overcrowding unhygienic conditions, exposure to animals and infections (e.g. hepatitis A, measles) or immunisation with BCG result in a lower prevalence of atopic manifestations (Shaheen et al., 1996; Matricardi et al., 1997; Strachan, 1997; Douwes et al., 2007; Simpson et al., 2008). According to that, it seems that since bacteria and viruses elicit Th1 immunologic responses, insufficient exposure to Th1 stimulators, results to insufficient down-regulation of Th2 immune responses and to the development of allergic reactions (Folkerts et al., 2000). However, it is a fact that the majority of asthma exacerbations in both children and adults with asthma are triggered by infectious organisms such as respiratory viruses, which are known to induce a Th1 response mediated by interferon-γ (IFN-γ) (Johnston et al., 1995) and this observation leads to the conclusion that not all infections are protective.

It is generally accepted that the development of asthma is the result of the interaction between genetic predisposition and environmental factors. In the latest years there is a dramatic change on two of the most important environmental factors. The first is the decreased incidence of infection, as a result of vaccination programs, sterile food preparations and the widespread use of antibiotics and the second is the alterations in diet especially regarding the consumption of saturated and unsaturated fats (Phipps et al., 2007). These two major alterations in the environmental conditions are believed to result in the underdevelopment of immunoregulatory mechanisms resulting in abnormal maturation of the adaptive immune system and to a shift towards Th2 response (Holt et al., 2005). Although there is still lack of full understanding of the generation of Th2 cell responses, there is emerging evidence showing that inappropriate stimulation of specific Toll-like receptors (TLRs) may play a role (Phipps et al., 2007). It is thus believed that microbial exposures may activate innate immune pathways through expression of TLRs and suppress Th2 cell immunity (Braun-Fahrlander et al., 2002; Ege et al., 2006).

2. Toll-like receptors

The first line response of an organism to identify and react to an invading pathogen is innate immunity, with several different mechanisms, pathways, proteins and/or cells included in this process. One of the most significant families of proteins that are able to identify and activate antigen presenting cells (APCs) are pattern recognition receptors (PRRs). They recognise conserved pathogen-associated molecular patterns (PAMPs, or microbe-associated molecular patterns (MAMPs)) and danger-associated molecular patterns (DAMPs) (Iwasaki and Medzhitov, 2010). One of the transmembrane PRRs is the TLR family of proteins (Cook et al., 2003).

The TLR family includes 10 different proteins that are either located in the cell membrane or in endosomes (Takeda and Akira, 2005) (Table 1). The first member of the family was identified in *Drosophila* (Hashimoto et al., 1988). Later on its antimicrobial potency was described (Lemaitre et al., 1996) and only shortly after, the identification of a human homolog was announced (Medzhitov et al., 1997). Discovery of TLRs has dramatically improved our knowledge of the molecular mechanisms involved in innate immunity, while there are increasing data suggesting their involvement not only in innate but also in activation and transition to acquired immunity (Iwasaki and Medzhitov, 2010).

TLRs are distributed in different cellular sites. More specifically TLR1, TLR2, TLR4, TLR5, TLR6 are mainly located in the cell membrane, while TLR3, TLR7, TLR8 and TLR9 have been shown to

Table 1
TLRs expression, PAMPs, DAMPs and signaling pathways (Werling and Jungi, 2003; Takeda and Akira, 2005; Cervantes et al., 2012).

	Cell distribution	PAMPs	DAMPs	Signal effector	Secreted Cytokines/ Chemokines	Alternate name	GeneID
TLR1	Cell surface Mo, MΦ, DC, B, EC	Triacylated lipoproteins peptidoglycans LPS	HSP60, HSP70 Gp96, HMGB1, proteoglycans	TIRAP, MyD88, Mal	ILs	CD281, TIL, TIL. LPRS5, rsc786	7096
TLR2	Cell surface Mo, MΦ, DC, B, EC, SMC	Triacylated lipoproteins peptidoglycans, LPS	HSP60, HSP70 Gp96, HMGB1, proteoglycans	TIRAP, MyD88, Mal	ILs	CD282, TIL4	7097
TLR3	Endosomes B, T, NK, EC DC, SMC	dsRNA, tRNA, siRNA	mRNA tRNA	TRIF	ILs, type I IFNs	CD283, IIAE2	7098
TLR4	Cell surface and endosomes Mo, MΦ, DC, MC, EC, SMC	LPS paclitaxel	HSP22, HSP60, HSP70, HSP72, Gp96, HMGB1, proteoglycans fibronectin, tenascin-C	TRAM, TRIF TIRAP, MyD88 Mal	ILs, type I IFNs	ARMD10, CD284, TLR –4, TOLL	7099
TLR5	Cell surface Mo, MΦ, DC, EC	Flagellin	Unknown	MyD88	IC	MELIOS, SLE1, SLEB1, TIL3	7100
TLR6	Cell surface Mo, MΦ, MC, B	Diacylated lipoproteins	HSP60, HSP70 Gp96, HMGB1, proteoglycans	TIRAP, MyD88, Mal	IC	CD286	10333
TLR7	Endosomes Mo, MΦ, DC. B	ssRNA, imidazoquinolines, guanosine analogs	ssRNA	MyD88	ILs, type I IFNs	TLR7-like	51284
TLR8	Endosomes Mo, MΦ, DC, MC	ssRNA, imidazoquinolines	ssRNA	MyD88	ILs, type I IFNs	CD288	51311
TLR9	Endosomes Mo, MΦ, DC, B,T, EC	CpG DNA, CpG ODNs	Chromatin IgG complex	MyD88	ILs, type I IFNs	CD289	54106
TLR10	Endosomes Mo, MΦ, DC	Profilin-like proteins	Unknown	MyD88	ILs	CD290	81793