Autoimmunity Reviews 12 (2013) 580–590

Contents lists available at SciVerse ScienceDirect

Autoimmunity Reviews

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

Review

p38 mitogen-activated protein kinase (p38 MAPK)-mediated autoimmunity: Lessons to learn from ANCA vasculitis and pemphigus vulgaris

Athanasios Mavropoulos [a,b], Timoklia Orfanidou [b], Christos Liaskos [b], Daniel S. Smyk [a], Charalambos Billinis [c], Miri Blank [d], Eirini I. Rigopoulou [e], Dimitrios P. Bogdanos [a,b,e,*]

[a] Institute of Liver Studies, King's College London School of Medicine at King's College Hospital, Denmark Hill Campus, London SE5 9RS, UK
[b] Cellular Immunotherapy and Molecular Immunodiagnostics, Institute of Research and Technology Thessaly, 41222, Larissa, Greece
[c] Department of Microbiology and Parasitology, Faculty of Veterinary Medicine, University of Thessaly, 43100 Karditsa, Greece
[d] The Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center, Tel-Hashomer, Israel
[e] Department of Medicine, University of Thessaly Medical School, Viopolis, Mezourlo 41110 Larissa, Greece

ARTICLE INFO

Article history:
Received 1 October 2012
Accepted 30 October 2012
Available online 30 November 2012

Keywords:
Autoantibody
Autoimmunity
Autoimmune disease
Signaling
Inflammation immunity

ABSTRACT

Evidence is beginning to accumulate that p38 mitogen activated protein kinase (p38 MAPK) signaling pathway plays an important role in the regulation of cellular and humoral autoimmune responses. The exact mechanisms and the degree by which the p38 MAPK pathway participates in the immune-mediated induction of diseases have started to emerge. This review discusses the recent advances in the molecular dissection of the p38 MAPK pathway and the findings generated by reports investigating its role in the pathogenesis of autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, and autoimmune hepatitis. Application of newly-developed protocols based on sensitive flow cytometric detection has proven to be a useful tool in the investigation of the phosphorylation of p38 MAPK within different peripheral blood mononuclear cell populations and may help us to better understand the enigmatic role of this signaling cascade in the induction of autoimmunity as well as its role in immunosuppressive-induced remission. Special attention is paid to reported data proposing a specific role for autoantibody-induced activation of p38 MAPK-mediated immunopathology in the pathogenesis of autoimmune blistering diseases and anti-neutrophilic antibody-mediated vasculitides.

Contents

Abbreviations: AIH, autoimmune hepatitis; ANCA, anti-neutrophil cytoplasmic antibody; DSG, desmoglein; DUSP, dual specificity phosphatase; EAE, experimental autoimmune encephalomyelitis; GADD45, growth arrest and DNA damage inducible gene 45; GC, germinal center; HSP, heat shock protein; IFN, interferon; IL, interleukin; LPS, liposacharide; MAPK, mitogen activated protein kinase; MAPKK, MAPK kinase; ., MAPK kinase kinase; ., MAPK phosphatase-1; PF, pemphigus foliaceus; PV, pemphigus vulgaris; RA, rheumatoid arthritis; TAB-1, transforming growth factor-activated protein kinase 1-binding protein 1; TCR, T-cell receptor; TGF, tumor growth factor; Th1, T-helper 1; TLR, Toll-like receptor; TNF, tumor necrosis factor; T-reg, T-regulatory; TTP, tristetrapolin.

* Corresponding author at: Department of Medicine, University of Thessaly Medical School, Viopolis, Larissa 41110, Greece. Tel./fax: +30 2410 555138.
E-mail address: dimitrios.bogdanos@kcl.ac.uk (D.P. Bogdanos).

1568-9972/$ – see front matter © 2012 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.autrev.2012.10.019

1. Introduction

Autoimmune diseases develop when immunological tolerance to self breaks down [1–4]. The mechanisms responsible for self-targeting immune responses are perplexing [5–9]. Initiating factors that have been implicated include genetic, epigenetic, environmental and infectious factors [5,10–14]. Irrespective of the initial trigger, autoimmunity arises when cells are under assault by effector T and B lymphocytes of the adaptive immune system [4,15,16]. Activation of the innate immune system long precedes that of the adaptive immune system and contributes significantly to the development of immune-mediated pathological processes [1]. The dynamic imbalance between pro-inflammatory and anti-inflammatory responses of the innate and adaptive immune system highly depends on the status of the expression and regulation of specific cytokines [1]. Promotion of the production of anti-inflammatory cytokines, and inhibition of the production and/or the action of inflammatory cytokines constitute the basis of most therapeutic interventions [17].

At the molecular level, cells sense the inflammatory microenvironment through specialized receptors and respond by triggering intracellular signaling circuits that transmit the necessary signals for appropriate reaction [18–20]. These consist of a complex network of protein kinases, where one activates the next by transferring phosphate groups of the ATP messenger to the hydroxyl accepting tyrosine, serine and threonine residues [21]. Therefore they are classified as either tyrosine (Tyr) or serine/threonine (Ser/Thr) kinases, with some exhibiting dual specificity as well. The stress-induced p38 mitogen activated protein kinase (MAPK) is an example of the above. An increasing number of studies have provided data suggesting that p38 MAPK plays a significant role in the pathogenesis of several immune-mediated diseases, including rheumatoid arthritis (RA), Sjögren's syndrome, systemic lupus erythematosus (SLE), inflammatory bowel disease (IBD) and psoriasis to name few [22]. The exact mechanism, however, and the degree by which the p38 MAPK pathway participates in the fore mentioned and other autoimmune diseases, has not been completely elucidated.

2. p38 MAPK: an introduction

The p38 MAPK was characterized and cloned back in 1994 while studying cellular responses and signaling pathway activation in response to environmental stresses such as hyperosmolarity, ultraviolet irradiation and heat shock [23,24]. Subsequent whole genome analyses have shown that up to 85% of the up-regulated gene expression due to stress is indeed related to the activation of p38 MAPK [25]. In the same year p38 MAPK was also independently described as a kinase phosphorylated in response to an endotoxin (liposacharide, LPS) and interleukin (IL-1) challenge, phosphorylating downstream targets such as hsp27 and regulating inflammatory gene expression [26,27]. p38 MAPK regulates the expression of tumor necrosis factor (TNF)-α, interferon-(IFN)-γ and other cytokines *via* transcriptional and post-transcriptional mechanisms [28–31]. It has therefore been suggested that inhibiting p38 MAPK would abrogate TNF-α, thus providing an anti-inflammatory therapeutic potential. The key role of TNF-α in the development of autoimmune disease is underlined by the success of therapies antagonizing the molecule either with monoclonal antibodies or soluble TNF receptors [17]. Predominant T-helper 1 (Th1) and T helper 17 (Th17) cytokine production is characteristic in many organ-specific autoimmune diseases [32], including RA, insulin-dependent diabetes mellitus, and experimental autoimmune encephalomyelitis (EAE). For instance, dysregulation of p38 MAPK activity specifically in autoreactive lymphocytes appears to be a modulator of EAE pathogenesis *via* enhanced IL-17 and IFN-γ expression [33].

Several pharmaceutical companies have invested heavily on the development of agents specifically inhibiting p38 MAPK activation. Due to the biochemical nature of activation, the ATP-binding pocket has become the focus of intensive design of these inhibitors that served as competitors for ATP-binding. SB203580, a pyridinyl imidazole and one of the prototypes of such compounds, is known to inhibit the p38 MAPK α and β isoforms [34,35]. α and β are two of the four p38 MAPK isoforms. The four isoforms share overall 75% homology and are differentially expressed among tissues [36]. p38α is strongly up-regulated in monocytes, macrophages, CD4 T cells, and neutrophils, while p38β is expressed mostly in endothelial cells. The γ isoform is expressed in myocytes and, together with p38δ, respond to inflammatory and toxic environmental triggers [37]. γ and δ p38 isoforms are insensitive to the pyridinyl imidazole inhibitors and this has so far not helped in the investigation of their functions [38]. An increasing amount of novel p38 MAPK inhibitors have been used in experimental studies and clinical trials and helped us to further define the role of p38 MAPK [39,40]. This review will concentrate on the role played by p38α, which is expressed mostly in tissues, and are tightly associated to both cytokine regulation and the inflammatory response.

3. To inhibit or not to inhibit p38 MAPK?

Extended biochemical analyses using pharmacological inhibitors, and transgenic mice expressing active or inactive forms of p38, have shed light into a multi-faceted role of this kinase in regulating many cellular processes other than inflammation. These processes include cell cycle regulation, apoptosis and cellular differentiation [41–45]. In clinical trials, many p38 kinase inhibitors were discontinued due to unacceptable toxicities, namely elevated liver enzymes with frequent outbreaks of skin rash [46]. Therefore, inhibition of the MAPK pathway as part of an anti-inflammatory therapy might not necessarily be best achieved by inhibiting p38 MAPK itself [47]. If its targeting is to be effective and safe, it must not compromise normal physiology, and the pathological inflammation should be tightly connected with the pathway. Therefore, before considering any therapeutic interventions, a top priority will be to answer for a well established association between the components of p38 MAPK signaling pathway and inflammatory gene expression in a given pathology. This depends to a great extent on the precise characterization of the biology of p38 MAPK activation, and how that differs between independent but cross-regulated cellular populations involved and contributing to the pathology of the targeted disease.

It is therefore possible that other targets upstream or downstream in the p38 kinase pathway may be targeted. This issue is highlighted by the advances in our current knowledge on the biochemistry of how exactly p38 MAPK phosphorylates and is being phosphorylated within cells. P38 MAPK pathway is not any more characterized by a single evolutionarily conserved phosphorylation cascade by a MAPK kinase kinase (MKKK) activating a dual-specificity MAPK kinase (MKK), which in turn induces a MAPK by phosphorylating both threonine and tyrosine residues in a Thr-Xxx-Tyr motif [48,49]. Recent evidence supports the existence of a classical activation pattern and two alternative ones (Fig. 1).

The classical p38 MAPK cascade is characterized by MEKK4 activation that serves as an upstream MKKK and activates MKK3, MKK4, or MKK6, which subsequently phosphorylates p38 MAPK at Thr180 and Tyr182 [50,51]. Among the different MAPKK subtypes are MKK3 and MKK6, which share approximately 80% amino acid homology and are believed to be the major participants in the activation of p38 MAPK [52,53]. This is already the first loop responsible for the diversity of the transmitted signals involving the selectivity of MKK3 and/or MKK6 in order to activate p38 MAPK under distinct circumstances and stimuli. Studies from MKK3 −/− and MKK6 −/− mice have revealed that both are required for full activation of p38 MAPK [54]. In line with an increased activation of p38 MAPK in synovial tissue of RA, MKK3 and MKK6 are also activated in the joints of patients with RA [55]. Additional studies went on to confirm that the MKK3/6 pathway is a primary mechanism for p38 phosphorylation in the rheumatoid synovium [56,57]. These and other studies have clearly indicated that the close interplay between MKK3 and MKK6 could