Review

# The Role of the p38 Pathway in Adaptive Immunity

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**Since its discovery in 1993, the mitogen-activated protein (MAP) kinase p38 has attracted much attention for its role in a wide range of cellular processes, many of which involve the immune system. Although p38 has been heavily implicated in the function of all type immune cells, research has tended focus on its role in innate immunity. In this review we attempt to highlight some of the major discoveries that have been made regarding p38's role in adaptive immunity, and also to discuss the possible future implications of these discoveries. *Cellular & Molecular Immunology*. 2007;4(4):253-259.**

**Key Words:** p38, MAPK, adaptive immunity, T cell, B cell

## Introduction

p38 (or p38α) was discovered and cloned while studying intracellular signaling pathways of inflammatory and stress responses (1-4). The structure of p38 revealed it to be a member of the mitogen-activated protein (MAP) kinase family. Three closely related proteins, p38β, p38γ (also known as ERK6 or SAPK3), and p38δ (SAPK4), were later identified and classified with p38α as a new MAP kinase family subgroup. Although the four mammalian p38 isoforms tend to share similar activation profiles, the kinetics and levels of activation of these isoforms have been found to vary (5-8). Additionally, these p38 isoforms only share around 60% sequence identity with one another and 40-45% sequence identity with other MAPK family members (9). This structural variance is believed to allow for the selective activation of different isoforms in different cell types by allowing specific combinations of upstream regulators and co-activators to activate a given p38 isoform under various physiological conditions and biological contexts (7, 10).

Like all other MAP kinases, p38 kinases are primarily activated by a tri-kinase cascade (although they can also be activated by some tri-kinase cascade-independent mechanisms (11-14)). At the top of this cascade are MAP3Ks (MAP kinase kinase kinases), followed by MKKs (MAP kinase kinases), and then MAP kinases (*i.e.*, p38). The MAP3Ks in this cascade are not very clearly defined, but should include TAK1, ASK1, and MLK3. The MKKs that activate p38 are primarily MKK3 and MKK6, with MKK4 also having been shown to induce p38α and p38δ activation in a few specific cell types, despite primarily serving as a JNK activator (6).

More than a dozen p38 substrates have been found, including protein kinases, transcription factors, and other proteins (Table 1). Phosphorylation of these substrates is essential for executing the biological functions of p38 group kinases, including the regulation of the cell cycle, cell development, cell differentiation, senescence, tumorigenesis, apoptosis, and immune responses (14-35). Although a simplified model can be drawn depicting the regulation and functions of the p38 pathway, the diverse role of the p38 pathway in different physiological and pathological processes has demonstrated that the regulation and function of the p38 pathway vary considerably among different cell types and biological processes. Therefore, a given function of the p38 pathway has to be understood within the context of a certain system and cell type. Here we attempt to review the current understanding of the p38 pathway in the context of the adaptive immune system.

## Role of p38 in T lymphocytes

*T lymphocyte development and differentiation*

The progression of early T cell (thymocyte) development is a complex process, beginning with hematopoietic stem cells in the bone marrow that migrate to the thymus and undergo a process of growth, differentiation, proliferation, and thymic selection. p38 activity is required early on in T cell development, but persistent activation of it has been found to block $CD4^-CD8^-$ double-negative (DN) T cells from progressing into $CD4^+CD8^+$ double-positive (DP) T cells (36, 37). Inactivation of p38 must occur in order to end this p38-induced cell cycle arrest, indicating the critical importance of

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Received Jun 12, 2007. Accepted July 25, 2007.

**Table 1.** Substrates and potential substrates of p38 MAPK

| | Substrates |
|---|---|
| Protein kinases | MK2 (4, 38), MK3 (39), MNK1 (40, 41), PRAK (42), MSK (43, 44) |
| Transcription factors | ATF2 (45), ATF1 (46, 47), Sap1 (48, 49), GADD153 (50), p53 (51), C/EBPβ (19), MEF2C (52), MEF2A (53), STAT1 (54), CHOP (50), ETS1 (55), Pax6 (56), ELK-1 (57), MITF (58) |
| Other protein substrates | cPLA2 (59), $Na^+/H^+$ exchanger isoform-1 (60), EE1A (61), Rab5:GDI complex (62), EGFR (63), Bcl-2 (64), Bcl-xL (64) |

p38 MAPK in regulating the differentiation and proliferation of early stage *in vivo* thymocytes (37).

Thymic selection, a process in which DP thymocytes become either single-positive (SP) $CD8^+$ or $CD4^+$ thymocytes or undergo self-destruction, follows this stage. Interestingly, despite the necessity of p38 inactivation for DN thymocytes to convert to DP thymocytes, both the positive and negative selection phases that follow this conversion appear to require the reactivation of p38 to some capacity.

During positive selection, DP thymocytes are screened for their ability to react with self-antigens complexed with major histocompatibility complex (MHC) molecules. The binding of T cell receptors (TCRs) to self-antigen/MHC molecules activates p38, along with other intracellular survival signals, which in turn protects thymocytes from apoptosis and also differentiates them into $CD8^+$ (CTL) or $CD4^+$ (Th) thymocytes (65, 66). Although it has been observed that p38 activity is not required for positive selection (36), as it appears that the MAP kinase ERK plays a more dominant role in positive selection (65, 67), it has been shown that severe inhibition of MAPK activity significantly impairs positive selection (65). Additionally, p38, unlike ERK, appears to have low-level constitutive activity in the absence of TCR engagement (65, 68-70).

During negative selection, SP thymocytes that survive positive selection are screened according to their level of reactivity to self-antigen/MHC molecules. Thymocytes that react too strongly receive an apoptosis signal and never become mature T cells. The role of p38 in negative selection is less clear than in positive selection, but *in vitro* observations in thymocytes treated with the p38 inhibitor SB203580 suggest that p38 kinase activation is required for negative selection as well (36).

*Helper T lymphocyte (Th)*

In addition to facilitating thymocyte selection, and hence the differentiation of DP T cells into Th cells, p38 appears to be involved in the differentiation of immature Th cells into effector Th1 and Th2 cells. The process begins when immature Th cells are stimulated by MHC-peptide complexes on antigen-presenting cells (APCs), which occurs *via* the TCR and CD28 costimulator (71). The Th cells then produce IL-2 and undergo rapid cell division, differentiating into mature effector Th cells.

Activation of p38 has been implicated in both Th1 and Th2 cell differentiation. In murine T cells, p38 is selectively activated in Th1 effector cells but not in Th2 cells. This selective activation plays a significant role in IFN-γ production, which is one of the aforementioned features that defines Th1 cells and distinguishes them from Th2 cells. Furthermore, MKK3 deficiency in mice has been found to correspond with a p38 deficiency-induced impairment of IFN-γ production, even when provided with antigen presenting cells from a wild-type B6 mouse. By contrast, transgene-encoded constitutively active MKK6 has been found to correspond to an increase in p38 activity and an increase in IFN-γ transcription. However, in human CD4 T cells, inhibition of p38 by an imidazole inhibitor or by expression of a dominant negative mutant of p38 reduced the production of IL-4, IL-5, and IL-13 in response to CD3 and/or CD28 stimulation (72, 73), indicating that p38 plays a crucial role in regulating Th2 cytokine production. In addition, inhibition of p38 by an imidazole inhibitor has been found to correspond to a decrease in nuclear translocation and phosphorylation of GATA3, which is critical for Th2 cytokine production (74, 75). The main MKKs upstream of TCR-mediated p38 activation in T cells are MKK3 and MKK6 (76). However, an MKK-independent p38 activation pathway has also been suggested based on the observation that p38 was found to be phosphorylated and activated through an alternate pathway that is independent of MKK3/6 activation (77). In this alternate pathway the SRC family kinases LCK and ZAP70 are sequentially activated upon TCR stimulation, and ZAP70 in turn phosphorylates p38 at residue Tyr323, not at residues Thr180 and Tyr182, which compose the well-known p38 dual phosphorylation motif. Phosphorylation at Tyr323 effectively activates p38 by inducing the autophosphorylation of Thr180 and Tyr182, judging from the observation that cells expressing Y323F mutant p38 and cells exposed to SB203580 exhibit impaired dual autophosphoryation. It is not known why this alternate pathway has evolved or how it is regulated; however, it seems probable that tissue- and/or stimuli-restricted p38 activation pathways might exist. Additionally, no evidence of Tyr323 phosphorylation in B cells has been found (78).

The downstream targets of the p38 kinase cascade that are responsible for IFN-γ production are believed to include members of the ATF transcription factor family, as c-jun/ATF2 sites within the IFN-γ promoter have been identified and a series of ATF bindings sites have been identified within the proximal and distal IFN-γ elements (two functionally active IFN-γ elements) (79, 80). However, ATF2 mutant cells have not been found to exhibit a decrease in IFN-γ production, which could imply that different factors, possibly ATF isoforms, can compensate for one another.

*Cytotoxic T lymphocyte (CTL)*

CTLs are important members of the immune system, serving

a role in destroying virus-infected and damaged cells, but little is known about the role that p38 plays in their function when compared to how much is known about the function of Th cells. However, it has been observed that p38 regulates IFN-γ production in CTL cells, as it does in Th cells (81), suggesting that p38 signaling is involved in IFN-γ induction pathways in both cell types (81).

*Regulatory T lymphocyte (Treg)*

A recent study by Steinbrink group has further demonstrated the critical importance of p38 in another facet of adaptive immunity, the coordination of the suppressor function of regulatory T (Treg) cells (also known as $CD4^+CD25^+$ T cells). Their study found that p38 induces $p27^{Kip1}$, which inhibits the cell cycle promoter cdk, effectively inducing and maintaining anergy in Treg (82). Furthermore, they found that the p38 inhibitor SB203580 led to cell cycle progression and a complete loss of regulatory function.

*Apoptosis in T lymphocyte*

Early *in vitro* studies showed that activation of the p38 pathway is essential for Fas-induced T cell apoptosis (83). Activation of p38 MAPK *in vivo* induced apoptosis in $CD8^+$ T cells, but not in $CD4^+$ cells, indicating that activation of the same pathway can lead to distinct phenomena in the different T cell subsets (81). $CD8^+$ T cell-specific apoptosis by p38 appears to occur due to a selective Bcl-2 reduction in this subset of T cells. Binding of the Fas ligand to its receptor Fas activates p38 in $CD8^+$ T cells (64). Fas-mediated activation of p38 in $CD8^+$ T cells induced the phosphorylation of Bcl-xL and Bcl-2 and prevented the accumulation of these antiapoptotic molecules within the mitochondria, which would result in the induction of apoptosis.

## Role of p38 in B lymphocytes

*B lymphocyte development*

In contrast to T lymphocytes, the requirement of p38α in B lymphocyte development, differentiation, and function is not well established. In the spleen, mature B lymphocytes develop from transitional type 1 (T1) and type 2 (T2) B cell precursors. Compared to T1 B cells, p38α, ERK, and Akt are predominantly activated following BCR (B cell receptor) crosslinking in T2 B cells. p38α, together with the other signaling molecules, is engaged in the stage-specific signaling pathway in the development process that induces the maturation of B cells (84).

*B lymphocyte activation*

CD40 is one of the major receptors that regulate B lymphocyte development and activation. CD40-mediated activation of B lymphocytes has been shown to induce activation of p38α, which resulted in the nuclear translocation of transcription factor NF-κB and ultimately promoted IgE isotype switching and facilitated the production of IgE (85, 86). p38α is required for CD40-induced gene expression and proliferation in B lymphocytes, as crosslinking of CD40 has been shown to rapidly induce the activation of p38α and its downstream kinase MK2, and as SB203580 treatment completely abolishes MK2 activation. CD40-induced expression of surface CD54/ICAM-1 was selectively reduced by SB203580, whereas CD40 and CD95/Fas were not affected by SB203580 (87). p38 is also linked to CD40 ligation-induced cytokines, such as IL-10, TNF-α, and LT-α, through the TRAF3-mediated signaling pathway (88). High-density microarray results from CD40-ligated murine B lymphocytes indicate that p38 may contribute by downregulating the expression of genes that negatively regulate cell growth, such as Rb2, Sap-1, and Ndr1 (89).

BCR is another major receptor that regulates B lymphocyte activation. Although among the MAP kinase pathways, ERK is primarily activated by BCR (90), the p38 pathway still plays a role in BCR-mediated cellular changes. BCR-mediated signaling in B lymphocytes promotes the activation of p38 and results in the phosphorylation of the downstream substrates cAMP response element binding protein (CREB) and MAPK-activated protein kinase 2 (MK2), and the inhibition of p38 by SB203580 significantly reduced the phosphorylation of these substrates (91). BCR-mediated activation of p38 in B cell line BT40 was abolished in Lyn/Syk-double deficient cells, but was not affected in PTK-deficient cells, indicating that activation of p38 is regulated by Lyn and/or Syk (92).

Interleukin-4 (IL-4) is a pleiotropic cytokine, which has an important function in the regulation of B cells during humoral immune responses (93). IL-4, together with CD40-mediated signals, stimulates the proliferation of B cells and induces the expression of CD23, MHC class II molecules, and induces the synthesis of IgG1 and IgE. Treatment of IL-4 and CD40 optimally induced the activation of p38, while the p38 inhibitor SB202190 and a dominant negative p38 mutant inhibited IL-4-induced expression of CD23 in B cells. Although p38 did not phosphorylate STAT6 (signal transducer and activator of transcription 6), it did directly regulate the transactivation activity of STAT6 (94). Another STAT6-independent IL-4 signaling pathway has been found to occur in B cells, instead of being mediated by SOCS3 (suppressor of cytokine signaling 3). SOCS3 expression was increased 9-fold within 5 hours of IL-4 treatment, and this induction was blocked by inhibitors of either JNK or p38 (95).

p38 is also involved in cellular responses induced by a number of other B lymphocyte activators. B lymphocyte stimulator (BLyS) induces human immunoglobulin switch recombinase and cytidine deaminase, and the induction of these enzymes are almost completely reversed by SB203580 treatment (96), suggesting that p38 is required for the immunoglobulin class switch process in B cells. Crosslinking of membrane IgM activates B lymphocytes, and p38 is also required for phosphorylation of CREB resulting in activation (91). Norepinephrin stimulation of the $\beta_2$-adrenergic receptor ($\beta_2$-AR) in B lymphocytes was found to be directly dependent on p38 MAPK-dependent upregulation of low-affinity Fc receptor for IgE (CD23) mRNA, and

consequently the rate of mature IgE mRNA transcription was increased. The $\beta_2$-AR-induced activation of p38 also increased IgE and CD23 release from the cell, suggesting that p38 could be a potential target for treating atopic diseases (97). Several cellular stress stimuli, such as osmotic shock, oxidative stress, chemical stress, and inflammatory cytokines, induced the production of 5-lipoxygenase, which was inhibited by the addition of the p38 specific inhibitor SB203580 (13).

Differential activation of p38, ERK, and JNK MAPKs might be related to the diverse cellular processes in B lymphocytes. These signaling pathways are simultaneously activated, but cells can be differentially activated in additional signaling contexts, depending on the signal activators (98, 99). These MAPKs phosphorylate different substrates and regulate the activation of different transcription factors such as AP-1, NF-κB, CREB, or ATF2.

*B lymphocyte apoptosis*

Ligation of CD40 in certain B cell lines may induce apoptosis and decrease proliferation (100-102). Arimura et al. reported that transfection of dominant negative JNK or treatment of SB203580 strongly reduced CD40-induced inhibition of B cell proliferation, suggesting that JNK and p38 are required for the CD40-induced inhibition of cell proliferation (103). In memory B lymphocytes, activation of p38 resulted in apoptosis by means of phosphorylation of Bcl-2 and release of cytochrome c, which could be prevented by the addition of a nerve growth factor (NGF) (104). It has also been reported that crosslinking of B lymphocyte membrane IgM, not membrane IgD, induces a delayed and sustained activation of JNK and p38 that results in apoptosis (105).

## Future perspectives

p38α, p38γ, and p38δ are very abundant in both T and B cells, and the expression of p38β is also detectable in T and B cells, and therefore the p38 signaling pathway must play significant roles in many cellular processes and responses in T and B cells. As we have summarized above, p38 activation is associated with T and B cell development and activation; however, there is also some data refuting the requirement of p38 in T and B cells development and proliferation. A chimeric p38-deficient mouse generated by using a RAG-deficient blastocyst complementation (RDBC) method showed normal T and B cell development, suggesting that p38 was dispensable for T and B lymphocyte development and proliferation (106). One of the possible interpretations of this observation is that other p38 group members can compensate for the loss of p38 in T and B cell development, since all p38 group members are expressed in T and B cells and the expression levels of p38γ and p38δ are much higher in T and B cells in comparison with many other cell types. Given the fact that the p38 pathway is essential for stress responses in all types of cells, the role of the p38 pathway in the stress responses of T and B cells is most likely to be essential too. The evidence showing that the p38 pathway plays an important role in gene expression in T and B cells is consistent with the observed functions of p38 in other cell types. We believe that the function of p38 in regulating gene expression is important in adaptive immunity. Because of the importance of adaptive immunity in human host defense and in immunity-related disease, and because p38 has long been considered to be a drug target in treating a number of diseases, more effort should be applied to investigate the function of the p38 pathway in adaptive immunity. Studying the p38 pathway in adaptive immunity will not only lead to a better understanding of the biology of lymphocytes, but will also provide useful information for the development of therapeutics that target p38.

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