MAP kinase activation in macrophages

K. Murali Krishna Rao

Pathology and Physiology Research Branch, Health Effects Laboratory Division, National Institute for Occupational Safety and Health, Morgantown, West Virginia

Abstract: Stimulation of macrophages by a variety of agents causes activation of mitogen-activated protein kinases (MAPKs). Activation of MAPKs by lipopolysaccharide involves CD14 and Toll receptors. Subsequent steps still remain to be explored. Tumor necrosis factor-α (TNF-α)-induced activation of MAPKs has been shown to involve the death domain proteins (TRADD, FADD, MADD) and TRAFs. Other molecules involved in this pathway include the protein kinases, ASK1, germinal center kinase (GCK), hematopoietic progenitor kinase 1 (HPK1), and GCK-related kinase (GCKR). Although, these pathways have been described in various cell types, their role in macrophages remains to be established. The availability of knockout mice and constitutively active and dominant-negative mutants of MAPKs should greatly enhance our understanding of this field. The activation of MAPKs seems to be different in cell lines compared with primary cells. Among the macrophages, cells from different compartments show different expression of receptors and signal transduction molecules. These differences may account for differences in MAPK activation and other phenotypic differences in macrophages from different compartments. Therefore, it is important to use primary cells for studying MAPK signal-transduction pathways, and the data from cell lines should not be extrapolated to primary cells. *J. Leukoc. Biol.* 69: 3–10; 2001.

Key Words: *Toll · TNF · TRAF · CD14 · GCK*

INTRODUCTION

In the last few years, the importance of mitogen-activated protein kinases (MAPKs) in mammalian cell biology has been established in innumerable studies using a wide variety of model systems. This field has been covered in several excellent reviews [1–4]. This review is focused on the role of MAPKs in macrophage physiology.

MAPKs constitute more than a dozen proteins belonging to three families, extracellular signal-regulated kinases (ERKs), p38 MAPKs, and c-Jun N-terminal kinase/stress-activated protein kinases (JNK/SAPKs) [1–4]. All three families of MAPKs have been shown to be activated in macrophages using a variety of stimuli (**Table 1**). A large number of these studies have been conducted in macrophage cell lines, yielding results much different from experiments conducted in primary cells. In this review, an attempt will be made to sort out these complexities and organize the current knowledge into some patterns that might make it easier to interpret the results.

THE ROLE OF CELL TYPE IN EXPERIMENTAL STUDIES

The experimental work in macrophages is conducted in a variety of cell lines of murine or human origin. These investigations revealed considerable differences in responses to stimuli between primary cells and different cell lines. Lipopolysaccharide (LPS) treatment induces activation of cytosolic phospholipase-2 (PLA2) in RAW 264.7 cells (a mouse monocytic cell line) but not in P338D1 cells (a mouse macrophage cell line). In particular, with respect to MAPKs, LPS stimulation causes activation of ERK in RAW 264.7 cells but not in P388D1 cells [39]. Similar differences are found between different cell lines in other kinase cascade systems, such as phosphatidylinositol-3 kinase (PI-3-kinase) and p^{70S6} kinase. Inhibition of DNA synthesis by rapamycin in bone marrow-derived macrophages (BMM) is much less than that observed in a colony-stimulating factor type 1 (CSF-1)-dependent cell line, BAC1.2F5 (a mouse macrophage cell line) [40].

In addition to differences between cell lines and primary cells, considerable differences exist among the circulating monocytes and macrophages, and among the macrophages residing in different tissues. The circulating monocyte possesses a markedly different functional phenotype relative to the tissue macrophage. The adhesive interactions encountered by the monocyte, en route to the inflammatory focus, generate signals that culminate in the expression of a proinflammatory phenotype marked by enhanced cytokine production. The process of adherence activates ERK1/2 and potentiates LPS-induced tumor necrosis factor-α (TNF-α) production. The adherence-dependent activation of ERK1/2 appears to be modulated by calcium/calmodulin-dependent protein kinase IV [41]. Another important modulator of macrophage function, RON receptor tyrosine kinase, is expressed in resident peritoneal macrophages but not in circulating monocytes or alveolar macrophages [42, 43]. Activation of RON inhibits LPS and interferon (IFN)-γ-induced macrophage inducible nitric oxide

Correspondence: K. Murali Krishna Rao, M.D., Box 2015, PPRB/HELD/NIOSH, 1095 Willowdale Road, Morgantown, WV 26505. E-mail: mir8@cdc.gov

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TABLE 1. MAPK Activation by Various Agents in Different Macrophage Cell Types

Cell type	Stimulus	MAPKs activated or influenced	Ref.
Human			
Alveolar macrophages	LPS	ERK, p38	[5, 6]
HL-60	PMA	ERK	[7]
Monocytes	FMLP or PMA	ERK1/2	[8]
Monocytes	LPS	ERK1/2	[9]
Monocytes	LPS	ERK, p38, JNK/SAPK	[10, 11]
THP.1 (monocytic)	LFA-1 & MAC-1 Cross-linking	ERK1/2	[12]
THP.1 (monocytic)	Mycoplasma fermentas lipoproteins	ERK, p38, JNK/SAPK	[13]
THP.1 (monocytic)	LPS	JNK	[14]
THP.1 (monocytic)	Bufalin (Na+-K+-ATPase inhibitor)	ERK	[15]
THP.1 (monocytic)	oxidized-LDL/immune complexes	ERK2	[16]
U937	PMA	ERK	[17]
Mouse			
BAC-1.2F5 (macrophage)	IL-16	p38, JNK/SAPK	[18]
BAC-1.2F5 (macrophage)	CSF-1	ERK1/2	[19]
Bone marrow macrophages	Cisplatin	ERK1	[20]
Bone marrow macrophages	LPS	JNK	[14]
Bone marrow macrophages	TNF plus IL-4	ERK, JNK/SAPK	[21]
Bone marrow macrophages	M-CSF or LPS	ERK1/2	[22]
Bone marrow macrophages	CSF-1	ERK1/2	[19, 23, 24]
Bone marrow macrophages	IFN-γ plus TNF-α	ERK, p38, JNK/SAPK	[25]
Bone marrow macrophages	TNF-α	ERK, p38, JNK/SAPK	[26, 27]
J774A.1 (monocytic)	Listeria monocytogenes	ERK1/2	[28]
J774A.1 (monocytic)	Yersinia enterocolitica	ERK, p38, JNK/SAPK	[29]
Peritoneal macrophages	Murine hepatitis virus strain 3	ERK, p38	[30]
Peritoneal macrophages	CSF-1	ERK1/2	[19]
RAW 264.7 (monocytic)	Lipocortin 1 (annexin 1)	ERK	[31]
RAW 264.7 (monocytic)	LPS	ERK1/2	[32]
RAW 264.7 (monocytic)	Mycoplasma fermentas lipoproteins	ERK, p38, JNK/SAPK	[13]
RAW 264.7 (monocytic)	Hyperoxia	ERK1/2	[33]
RAW 264.7 (monocytic)	LPS	ERK, p38, JNK/SAPK	[34–36]
RAW 264.7 (monocytic)	LPS	JNK	[14]
RAW 264.7 (monocytic)	TNF	ERK, p38	[37]
Rat			
Peritoneal macrophages	LPS plus sodium salicylate	ERK, JNK/SAPK	[38]

Abbreviations: FMLP, *N*-formyl-methionyl-leucyl-phenylalanine; IL-16, interleukin-16; LDL, low-density lipoprotein; M-CSF, macrophage colony-stimulating factor (also known as CSF-1); PMA, β-phorbol 12-myristate 13-acetate.

synthase (iNOS) production and iNOS mRNA accumulation [44]. Obviously, such an effect will not be demonstrable in circulating monocytes and alveolar macrophages, the cell types that do not express RON receptor.

Also, differences in interleukin (IL)-1β regulation have been demonstrated between monocytes and macrophages [45]. Other studies have demonstrated differences in signaling pathways based on the maturation stage of macrophages [46]. A variety of differences have been defined between human peripheral blood monocytes and alveolar macrophages [47–50]. Therefore, the use of the generic term macrophage in studies involving signal transduction pathways may lead to confusion. So in this review, effort is devoted to specifying the macrophage cell type that has been used. Such practice may aid in clarifying the results from various studies.

The most commonly used stimuli to study MAPKs activation in macrophages are the bacterial cell wall LPS and the proinflammatory cytokine TNF-α. LPS has been shown to activate all three families of MAPKs in a variety of macrophage cell types [9, 11, 14, 32, 34, 35]. Similarly, all three MAPKs have been implicated in the macrophage activation induced by TNF-α [21, 51, 52].

SIGNAL TRANSDUCTION EVENTS ASSOCIATED WITH MAPKs ACTIVATION WITH LPS STIMULATION

Despite several studies using LPS, the signal transduction events utilized by this bacterial product remain to be defined (**Fig. 1**). Various pathways of activation following LPS stimulation have been reviewed previously [53]. LPS first interacts with a plasma protein, LPS-binding protein, and is presented to a surface receptor, CD14, which facilitates LPS signaling [54]. In addition to CD14, a second set of receptors, Toll-like receptors (TLRs), have been shown to transduce bacterial cell

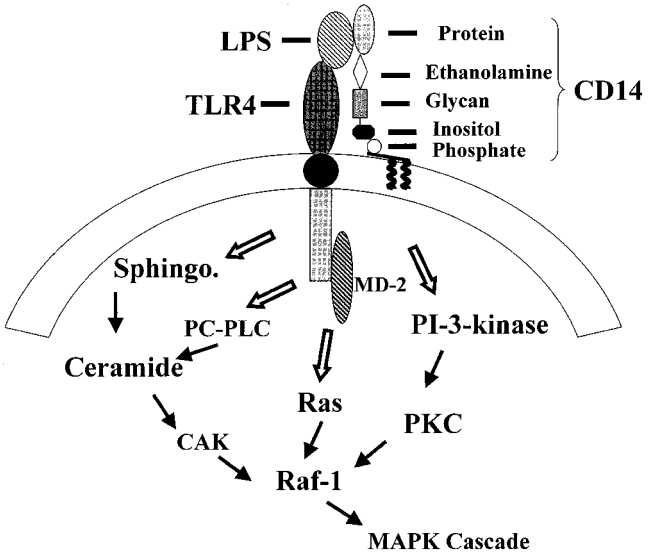

Fig. 1. A schematic representation of the molecules implicated in MAPK activation in cells of macrophage/monocyte origin following LPS stimulation.

wall-induced signal transduction in macrophages [55, 56]. TLRs are mammalian homologues of *Drosophila* Toll receptor and are thought to have a role in innate immunity [55, 57]. TLRs have been demonstrated in human monocytes [58] and mouse peritoneal macrophages [59]. TLR4 is identified now as the signaling receptor for LPS [60–62]. Association of LTR 4 with another molecule, MD-2, is required for LPS recognition [59]. This association with MD-2 is essential for activation of MAPKs and phosphorylation of the transcription factor Elk-1 [63]. A role for Toll receptors in MAPK activation is demonstrated further by the observation that ectopic expression of hToll (TLR4) in human embryonic 293 cells causes activation of JNK/SAPK [58].

LPS has been shown to activate protein kinase C (PKC) in macrophages [64]. In human monocytes, the protein kinase C-zeta isoform seems to be activated through a PI-3-kinase-dependent pathway [65]. PKC in turn has been shown to activate MAPK pathway in a manner independent of Ras but dependent on Raf [66]. Further evidence for involvement of PKC in MAPK activation is provided by the fact that defective LPS-dependent ERK1/2 activation in endotoxin-tolerant mice can be reversed by direct PKC stimulation [67]. In human alveolar macrophages, activation of phosphatidylcholine-specific phospholipase C (PC-PLC) induced by LPS has been linked to activation of ERK1/2 [5]. Other pathways that have been implicated in ERK activation by LPS include *ras* and Raf-1-mediated events [68–70]. Another pathway for LPS action is the activation of sphingomyelinase to release ceramide, which then activates ceramide-activated protein kinase (CAK). Raf-1 is a target for CAK, providing an entry into the MAPK pathway [71]. Although the exact pathways for activation of MAPKs in macrophages following LPS stimulation still need to be defined, clearly CD14 and TLR-mediated events are involved in the process.

SIGNAL TRANSDUCTION EVENTS ASSOCIATED WITH MAPK ACTIVATION WITH TNF-α STIMULATION

TNF-α binds to two distinct TNF receptors of 55 kD (TNFR1) and 75 kD (TNFR2) (reviewed in [72]; **Fig. 2**). Binding TNF-α to its receptor initiates association of a number of TNF receptor-associated proteins to the cytoplasmic end of TNF receptors. These include TNFR1-associated death domain protein (TRADD), which recruits Fas-associated death domain (FADD, also known as MORT1) protein and TNF receptor-associated factor 2 (TRAF2) [72, 73]. TRAF2 contains a conserved C-termial region termed the TRAF domain, which interacts with TRADD and an N-terminal ring finger required for signaling the activation of nuclear factor-κB (NF-κB) and JNK/SAPK [74–76]. Another step in the activation of JNK/SAPK through TRAF2 is involvement of the apoptosis signal-regulated kinase 1 (ASK1) [77]. A third death domain-containing protein, MAP kinase-activating death domain protein (MADD), has been shown to activate ERK in a specific manner [78]. However, all these observations have been made in different cell types, other than macrophages, and their relevance to macrophage function remains to be established. It has been shown that activation of SAPK also involves three other protein kinases, germinal center kinase (GCK) [79, 80], hematopoietic progenitor kinase 1 (HPK1) [81, 82], and GCK-related kinase (GCKR) [83]. HPK1 has a limited range of tissue expression, whereas GCK, although widely expressed, is only affected marginally by TNF [80]. GCKR is widely distributed and is activated by TNF [83, 84]. Evaluating the presence and activation of these kinases in macrophages from different compartments may prove useful in understanding the molecular basis for differences in macrophages from different sources.

ROLE OF MAPKs IN MACROPHAGE DIFFERENTIATION AND PROLIFERATION

Activation of MAPKs has been demonstrated with agents that induce proliferation and activation. BMM proliferate in re-

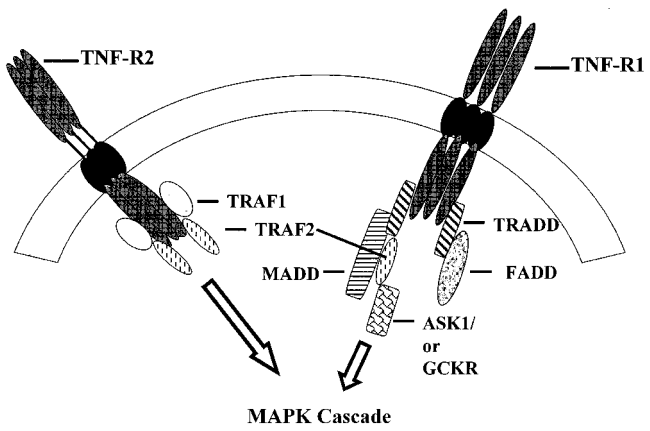

Fig. 2. A composite schematic representation of the various molecules implicated in MAPK activation in different cell types following TNF stimulation. The roles of many of the molecules in monocyte/macrophage cell activation remain to be established.

sponse to specific growth factors, such as colony-stimulating factor-1 (CSF-1, also called M-CSF). CSF-1 is required for the development of monocytes/macrophages from progenitor cells and for the survival and activation of mature macrophages. CSF-1 activates MAPKs in BMM [19, 22–24]. Furthermore, when cells are stimulated with activating factors, such as LPS, macrophages stop proliferating and produce proinflammatory cytokines. However, both types of stimuli induce activation of ERK. Differences in the time and duration of ERK activation have been proposed as mechanisms for distinguishing between pathways directed toward proliferation versus activation [22]. The termination of ERK activity may be a result of simultaneous transient expression of mitogen-activated protein kinase phosphatase-1 (MKP-1), which correlates with the inactivation of ERK1/2 [85]. A role for MAPKs in the regulation of cell proliferation is supported by the observation that ERK and p38 participate in the regulation of D-type cyclins, which are essential and rate-limiting for G1-phase progression in normal mammalian cells [86]. However, other investigators question if ERK activation is absolutely required for macrophage proliferation [19]. Evidence supporting a role for MAPKs in macrophage differentiation comes from studies in promyelocytic cell lines, HL-60 and U937. Treatment of HL-60 cells with phorbol 12-myristate 13-acetate (PMA) results in growth arrest and differentiation toward the macrophage lineage [7]. PMA causes rapid activation of ERKs, and this activation is believed to be essential for PMA-induced differentiation of HL-60 cells. PMA induces the expression of cyclin-dependent kinase inhibitors, p21(WAF) and p27(kip1), which are modulated by an inhibitor of the ERK cascade (PD 98059). This was taken to mean that a link exists between ERK activation and p21(WAF) and p27(kip1) induction in the process of terminal differentiation [7]. ERK has also been implicated in PMA-induced differentiation of U937 cells (a human monoblastoid leukemia cell line), where it has been shown to phosphorylate a TATA-binding protein and thereby induce gene transcription leading to macrophage differentiation [17]. However, a PMA-resistant variant of the U937 cell line (UT16) shows activation of PKC, Raf-1, and ERK/MAP kinases similar to parental cell line but fails to differentiate into a monocytic cell lineage [87]. Recent observations indicate that prolonged activation of mitogen-activated protein kinase pathway is required for macrophage-like differentiation of a human myeloid leukemic cell line [88]. Other studies indicate that activation of p38 may lead to apoptosis or cell activation, depending on what other factors, such as ERK1, activator protein-1 (AP-1), and NF-κB, activate coordinately [89]. Clearly, the regulation of cell proliferation is more complicated than simply activation of MAPKs. CSF-1 causes increased expression of protein phosphatase-2A (PP2A) in BMM, and inhibition of PPA2 with okadaic acid prevents DNA synthesis in a dose-dependent manner [23]. Okadaic acid does not affect the basal or CSF-1-induced ERK activity in BMM, indicating that PPA2-dependent cell proliferation could be dissociated from ERK activation in macrophages [23]. Therefore, it is reasonable to assume that a series of events have to take place for the final emergence of a phenotype and several checks and balances exist, which finely regulate the response to a given agent.

DEVELOPMENTAL CHANGES IN MAPKs IN MACROPHAGES

Four isoforms of p38 MAPK (p38α, β, γ, δ) have been described. In monocytes, p38α is the predominant form, expression of p38δ is low, and p38β is not detected. In macrophages, p38α and p38γ are abundant, but p38β is absent. It is suggested that p38α plays a major role in the inflammatory response [90]. Other investigators, however, show a coordinate activation of all four endogenous p38 isoforms and consider all may play an important role in inflammation [91].

Further understanding of the role of MAPKs in macrophage differentiation and proliferation is being gained by studying the embryonic stem cells. Suppression of the protein tyrosine phosphatase SHP-2 and ERK signaling has been shown to promote self-renewal in mouse embryonic stem cells [92]. Many mouse gene knockout models are being developed, and even though some of the genetic disruptions of MAPK pathways lead to embryonic lethal mutants, stem cells from the embryos are being used to study the role of MAPKs in various developmental processes [93, 94].

CONSEQUENCES OF MAPKs ACTIVATION

After phosphorylation and activation, the MAPKs translocate to the nucleus where they phosphorylate and activate several targets. Transcription factors are the major targets for MAPKs. The transcription factors phosphorylated include ELK1 [95, 96], ATF-2 [97], and c-Jun [98], and they in turn induce transcription of several early genes involved in cell activation, proliferation, and transformation. MAPKs have been recognized generally for their role in mediating signal-transduction events regulating transcription, but recent studies implicate them in the regulation of translational events also [99]. The eukaryotic initiation factor, eIF4E, is phosphorylated by MAPKs [100]. Specifically, the p38 MAPK inhibitor, SB 203580, blocks the phosphorylation eIF4E [101]. It needs to be emphasized that several proinflammatory mediators are under transcriptional as well as translational control; these include NO [102], TNF [99], and IL-β [103]. Therefore, MAPKs may be involved at transcriptional and translational regulation of proinflammatory mediators.

NEWER TECHNIQUES FOR STUDYING MAPK FUNCTIONS

In the past, most of the studies resorted to chemical inhibitors for studying MAPK regulation. But, subsequent studies indicated that the drugs employed could inhibit or activate other protein kinases under some experimental conditions [104, 105]. Molecular biology techniques provide a more precise way for activating or inhibiting specific enzyme activities. Targeted disruption of MAPK kinases (MKKs) has been accomplished. MKK4 gene disruption causes marked defects in JNK activation and early embryonic death [106–108]. However, stem cells from the embryos can be used for studies of signal

transduction as mentioned above. Targeted disruption of MKK3 revealed the importance of TNF-induced cytokine expression in fibroblasts [109]. Defective thymocyte maturation has been demonstrated in ERK1 knockout mice [110]. Such animals can be used for studying the effects of specific MAPK gene disruptions in macrophage function.

Other strategies to study MAPK function include making constitutively active MKKs [111], constitutively active MAPKs by fusing with constitutively active MKK [112], and constitutively activating MAPKs by overexpressing tyrosine kinases such as c-fes [113]. A number of vectors have been developed to overexpress activated MAPKs or dominant-negative mutants. Such vectors are available for JNK [114], p38 [115], and ERK [116]. These methodical advances need to be applied to study the role of MAPKs in macrophage function and have the potential to yield important insights into their function in this cell type.

CONCLUSION

As shown in Table 1, all three MAPKs have been shown to undergo activation in several macrophage cell types using a variety of stimuli. MAPKs have been implicated in proliferation, differentiation, and activation of macrophages. The response appears to be context-specific. For example, stimulation with MCF causes phosphorylation of MAPKs and proliferation in BMM, but stimulation with LPS in monocytes causes phosphorylation of MAPKs, inhibits proliferation, and causes activation. In addition, the response to stimuli depends on the maturation state of the macrophages. This may be because of differences in the expression of various signal-transduction molecules. For example, the expression of PKC isoforms is different in blood monocytes compared with alveolar macrophages [49]. Also, human alveolar macrophages are markedly deficient in REF-1 and AP-1-binding activity [47]. Differences in RON receptor expression have been mentioned above.

Several studies indicate that all three MAPKs are activated by LPS in macrophage cell lines such as RAW 264.7, J774.A, and NR8383 cells (see Table 1). But this may not be the case in primary cell lines. In human alveolar macrophages, ERK and p38 activation have been demonstrated [6]; and although JNK/SAPK activation has not been studied specifically, simultaneous inhibition of ERK and p38 kinase pathways reduces cytokine expression to near control levels, suggesting that JNK/SAPK pathway by itself is not sufficient for cytokine expression [6]. Our studies indicate that in rat alveolar macrophages, LPS causes activation of only ERK and that inhibition of ERK by PD 98059 abrogates NO and TNF-α production (unpublished results). In view of these observations, caution is needed in extrapolating data from cell lines to primary cells. In fact, the role of MAPKs in the regulation of inflammatory cytokine biosynthesis was discovered using the cytokine-suppressive anti-inflammatory drugs in a human monocytic cell line, THP.1. In that study, the authors acknowledge that the cell line was more sensitive to inhibition by the drugs than human monocytes [117]. It should be noted that the suppression of cytokine production by p38 MAPK inhibitors has been shown to occur at a post-transcriptional step in this cell line.

In view of the differences enumerated in various cell types, the signal transduction events associated with MAPK activation cannot be extrapolated from one cell type to another. In fact, differences in these signal transduction pathways may be the key to the phenotypic variation among the cells of monocytic/macrophage lineage in various compartments. Many of the signal transduction events associated with TNF receptor activation have been demonstrated in different cell types, and there are very few studies in macrophages specifically. Study of the expression of various TRAFs and death domain proteins may be useful in understanding the differences in macrophage phenotypes. These studies should be conducted in primary cells, rather than cell lines, to approach more closely the situations that may be valid *in vivo*. The availability of knockout mice and constitutively active and dominant-negative mutants of MAPKs should enhance our understanding of this field greatly.

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