[Frontiers in Bioscience 13, 5866-5879, May 1, 2008]

MSK activation and physiological roles

J. Simon C. Arthur

MRC Protein Phosphorylation Unit, College of Life Sciences, University of Dundee, Dundee, DD1 5EH, UK

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1. ABSTRACT

Mitogen and stress activated protein kinase (MSK) 1 and 2 are nuclear serine/threonine protein kinases that are activated *in vivo* downstream of either the ERK1/2 or p38 mitogen activated protein kinase (MAPK) cascades. MSKs contain two kinase domains, an N-terminal kinase domain related to the AGC kinase family, and a C-terminal kinase domain related to the CaMK family. The upstream MAPK phosphorylates the C-terminal domain, which then phosphorylates and activates the N-terminal domain. Once activated, the N-terminal domain phosphorylates substrates. MSKs do not have a precisely defined substrate consensus sequence, however the do have a preference for a basic cluster prior to the phosphorylated residue. In cells MSKs phosphorylate several substrates including CREB, NFκB, HMGN1 and histone H3. The major role of MSKs appear to be in the regulation of immediate early (IE) genes, and consistent with this the transcription of several CRE dependent IE genes is compromised in MSK knockouts. The physiological roles of MSKs still remain to be completely determined, however recent work has suggested a role for MSKs in neuronal synaptic plasticity and in regulating cytokine production in the innate immune system.

2. INTRODUCTION

Mitogen activated protein kinase (MAPK) cascades are key regulators of many cellular processes, including survival, proliferation and differentiation. Misregulation of these cascades has been implicated in several pathologies including cancer, neurodegeneration and autoimmune disorders. Fourteen MAPKs have been described in mammalian cells. These can be divided into four groups: the classical MAPKs (ERK1 and 2), p38 MAPKs, JNKs and atypical MAPKs, such as ERK3, ERK4, ERK5 and ERK8 (1-3). Of these, ERK1/2 and p38α have been shown to activate several downstream kinases, while ERK3 and ERK4 have a role in MK5 (or MAPKAP-K5) activation (4-6). ERK1/2 activates the RSK family of kinases while p38 activates MK2 (also known as MAPKAP-K2) and MK3. Two other groups, MNKs and MSKs, are able to act downstream of either ERK1/2 or p38. This review will focus on the activation mechanism of MSKs and their potential physiological roles.

MSK (mitogen and stress activated protein kinase) 1 was first described in 1998 as a kinase that could be activated in cells by either ERK1/2 or p38 (7). Shortly after this, another group also reported the cloning of MSK1

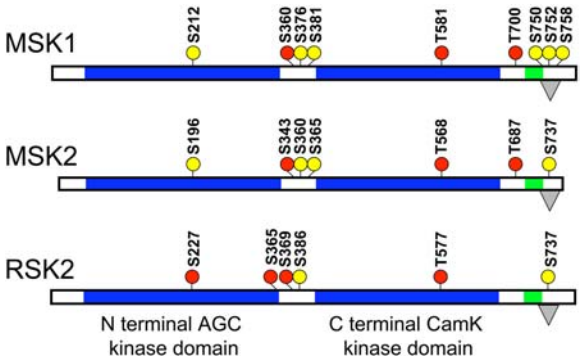

Figure 1. Domain structure of MSKs. MSK1 and MSK2 contain two kinase domains (blue rectangles) in a single polypeptide. The C-terminus also contains a nuclear localisation sequence (green rectangles) and MAPK docking sequence (grey triangle). For activation, MSKs require phosphorylation of three conserved sites by the upstream MAPK kinase (red circles) and the autophosphorylation of further sites (yellow circles). MSKs are most similar to RSKs, and the domain structure of RSK2 is shown for comparison.

(8). In overexpression studies, MSK was found to be predominantly localised to the nucleus in both serum starved and stimulated cells (7, 9). Consistent with this subcellular localisation, the first reported substrate for MSKs was the transcription factor CREB (7, 9). In addition to MSK1, a related isoform, termed MSK2 or RSK-B has also been identified (7, 9). The human isoforms of MSK1 and MSK2 are 64% identical to each other, and they show significant similarity to the RSK kinases. Like RSK, MSKs contain two kinase domains in the same protein, separated by a short linker. The N-terminal domain belongs to the AGC kinase family, while the C-terminal domain to the CaMK family (6) (Figure 1).

Orthologues of mammalian MSKs can be found in *Danio rerio*, *Xenopus* and *C. elegans*, however MSKs have not been identified in yeast or plants. The closest orthologue in *Drosophila* is the kinase Jil-1, which has a similar N-terminal kinase domain but divergent C-terminal kinase domain (10). Unlike mammalian MSKs, which are not essential for development, Jil-1 is essential for viability in *Drosophila* (11). It is not currently clear if Jil-1 acts downstream of the same signals as mammalian MSKs, and may not be a true functional orthologue.

3. ACTIVATION OF MSKS

Depending on the cell type and stimulus, MSK activation *in vivo* is dependent on either the ERK1/2 or p38 MAPK cascades, and stimuli that activate these cascades will usually result in MSK activation (7-9, 12). *In vitro*, both ERK1/2 and p38 can directly phosphorylate the same sites on MSK1, and this results in MSK1 activation (7, 13). In cells, the requirement for ERK1/2 or p38 in MSK activation was originally shown by the use of small molecule inhibitors that block the ERK1/2 or p38 cascades (12) (7, 14). The function of the ERK1/2 cascade has been widely studied through the use of inhibitors, such as PD98059, U0126 or PD184352, that block MEK1 and 2, the upstream activators of ERK1/2 (15). For stimuli, such as EGF or PMA, which are strong activators of ERK1/2 but only weak activators of p38, PD98059, U0126 and PD184352 have all been shown to block the activation of MSK1 and MSK2 (7, 12). These inhibitors do not distinguish between the functions of ERK1 and ERK2, and it has not been determined if one or both of these kinases are able to activate MSKs *in vivo*. When used at high concentrations MEK1/2 inhibitors have been shown to inhibit MEK5, and therefore to block the activation of ERK5 in addition to ERK1/2 (16, 17). A role for ERK5 in MSK activation appears unlikely however as MSK activation can be blocked at low concentrations of PD184352 that will still inhibit ERK1/2 activation but which do not affect ERK5 activation (13).

MSKs are also activated by stimuli, such as UV-C and anisomycin, that are strong p38 activators, but which do not significantly activate ERK1/2 (12) (7, 14). In these circumstances MSK activation is completely blocked by the p38 inhibitor SB203580. Four isoforms of p38 have been described, p38alpha, beta, gamma and delta. SB205680 inhibits both p38alpha and p38beta, but not p38gamma or p38delta (15). *In vitro*, both p38alpha and p38bata can phosphorylate MSK1, suggesting that both p38alpha and beta isoforms could play a role *in vivo* (7). The use of embryonic fibroblasts from p38alpha and p38beta knockout mice has however demonstrated that p38beta knockout has no effect of MSK1 activation, but that p38alpha knockout abolishes p38 dependent activation of MSK1 (18, 19). It therefore seems likely that p38alpha is the major p38 isoform *in vivo* responsible for MSK activation.

Some stimuli, such as NGF or TNF have the potential to activate both ERK1/2 and p38 and in these circumstances it appears that both pathways contribute to MSK activation. For these stimuli, either PD184352 or SB203580 alone can only partially inhibit MSK activation, but a combination of both PD184352 and SB203580 can completely block MSK activation (7, 20). Many additional stimuli have now been shown to activate MSKs in cell culture, including Interleukin 1 (21-23), lysophosphatidic acid (24), endothelin-1 (25), arsenic trioxide (26) and oxidative stress (27, 28). In animals exercise has been shown to induce MSK activation in skeletal muscle (29) and light activates MSK1 in the suprachiasmatic nucleus in the brain (30).

The activation mechanism of MSKs was originally thought to be similar to that of RSK. In the case of RSK, the upstream MAPK, ERK1/2, is recruited via a docking domain. ERK1/2 then phosphorylates two sites, the T loop site in the C-terminal kinase domain and a further site in the linker. This activates the C-terminal kinase domain, which then phosphorylates the hydrophobic motif of the N-terminal kinase domain. The phosphorylation of the hydrophobic motif is required to recruit another kinase, PDK1, which then phosphorylates the T loop of the N-terminal kinase domain. This activates the N-terminal domain, which then phosphorylates downstream substrates (31-33).

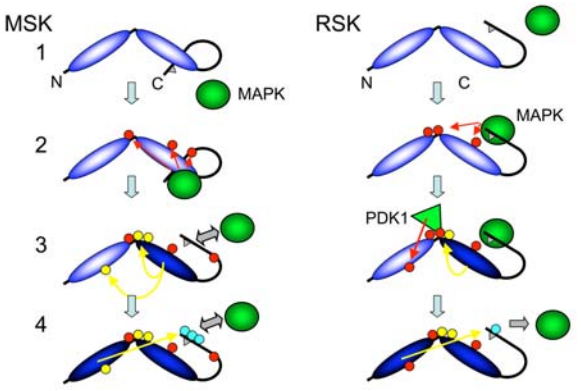

Figure 2. MSK1 activation. MSKs are activated via a sequential series of phosphorylation sites. Binding of the upstream MAPK (either ERK1/2 or p38) to MSK1 occurs via the C-terminal MAPK docking site. The upstream kinase then phosphorylates three sties in MSK1 (red circles); a site in the linker between the two kinase domains (Ser360), the T loop of the C-terminal kinase domain (Thr581) and a site in the C-terminus (Thr700). The phosphorylation of Thr700 acts to reduce the inhibition of the C-terminal kinase domain by the autoinhibitory C-terminal sequence. In combination with Thr581 phosphorylation this activates the C-terminal kinase domain. Following this, the C-terminal kinase domain then phosphorylates two sites in the linker region (Ser376 and 381) as well as the T loop of the N-terminal kinase domain (yellow circles). This results in the activation of the N-terminal kinase domain, which then both phosphorylates substrates as well as autophosphorylating the C-terminal tail (blue circles). Residue numbers are for human MSK1. The activation of MSK is similar to RSK although there are several significant differences. In RSK, phosphorylation of the linker recruits another kinase PDK1 that then phosphorylates the T loop residue in the N-terminal domain of RSK. Phosphorylation of the C-terminus by the N-terminal domain in RSK also promotes the dissociation of RSK from the upstream MAPK

The activating phosphorylation sites in RSK are completely conserved in MSKs, and MSK1 was originally cloned as a potential PDK1 substrate (7). Consistent with this it has been shown that when the isolated N-terminal domain of MSK1 is cloned and expressed, it can be phosphorylated and activated by PDK1 (34). However, analysis of PDK1 knockout or knockin embryonic stem cells has demonstrated that while PDK1 was essential for the activation of RSK, PDK1 was not required for MSK1 activation (32, 35). Subsequent analysis of the activation mechanism of MSK1 revealed that while it is similar to RSK, significant differences, as described below, exist between MSK and RSK activation (13, 36) (Figure 2).

The domain structure of MSK1 is shown in Figure 1A. MSK1 is made up of a short N-terminal sequence, N-terminal kinase domain, linker sequence, C-terminal kinase domain followed by a C-terminal tail. The C-terminal tail fulfils at least three functions, it contains both the nuclear localisation sequence and MAPK docking sequence and it can also act as an auto inhibitory sequence (36). Many MAPK substrates have been shown to contain MAPK docking motifs, and the precise sequence of this motif determines which MAPK can bind to the substrate protein (37). Interestingly in the case of MSKs, the same docking sequence is able to bind to either ERK1/2 or p38, and mutation of this sequence blocks MSK activation by either ERK1/2 or p38 (13). On binding to MSK1, ERK1/2 or p38 phosphorylate three sites, Ser360, Thr581 and Thr700 (36). Thr581 is in the T loop of the C-terminal kinase domain and is essential for the activation of this domain. Thr700 is in the C-terminal tail, and Thr700 phosphorylation acts to relieve an auto-inhibition of MSK1 by its C-terminal tail. Ser360 phosphorylation is not essential for MSK activity but probably acts to help maintain the other phosphorylation sites in MSK (13, 36). Once active the C-terminal kinase domain phosphorylates Ser376 (equivalent to the hydrophobic motif of RSK) in the linker region, and this is essential for activation of the N-terminal domain. Unlike RSK, in MSK1 the C-terminal kinase domain is also able to phosphorylate Ser212 in the T loop of the N-terminal domain. Together with Ser376 phosphorylation, this activates the N-terminal domain. The C-terminal domain can also phosphorylate Ser381, although this is not critical for activity (13, 36).

Once active the N-terminal domain is then responsible for the phosphorylation of substrates. In addition the N-terminal domain also phosphorylates three sites in the C-terminus of MSK1, although the function of these sites is unclear. Phosphorylation of an analogous site in RSK promotes the dissociation of RSK from ERK (38), however phosphorylation of this site does not appear to play the same role in MSK1 (13). Four further phosphorylation sites have also been identified in MSK1, however the function of these sites, and the kinases responsible, are unknown (36).

The phosphorylation sites in MSK2 have not been mapped, however the key sites identified in MSK1 are conserved in MSK2. Mutagenesis studies of MSK2 has confirmed the importance of many of these sites in MSK2 activation (14, 20), suggesting that the overall mechanism is similar in MSK2 to MSK1.

4. MSK INHIBITORS

Several compounds have been reported to inhibit MSKs *in vivo*. H89 and Ro 318220 were the first inhibitors found to block MSK activity, however neither compound is very specific for MSKs (20). H89 was originally developed as a PKA inhibitor, and is able to inhibit PKA at lower concentrations than required to block MSK. H89 also inhibits S6K1 and ROCK-II with a similar potency to MSK1. In addition, H89 inhibits RSK and PKB, although the *in vitro* IC50 was 10 fold higher than for inhibition of MSK1 (15, 39). Ro 318220 was originally developed as a PKC inhibitor, however it was subsequently found to inhibit MSK1, S6K1, RSK and GSK3 with a similar potency to PKC (15, 39). While both these compounds have been used to study MSK in cells, care must be taken in the interpretation of these results for two reasons. Both

Figure 3. MSK phosphorylation site sequences. The sequence of the sites phosphorylated *in vitro* by MSKs in CREB, ATF1, histone H3, NFκB, LKB1, nur77 and ER81 were aligned. Conserved arginines are highlighted in black and lysines in grey. Of the proteins listed, LKB1 and nur77 are not *in vivo* substrates for MSK1, while it is not clearly established if ER81 is an *in vivo* substrate. The ability of RSK and PKA to phosphorylate these sites *in vitro* is also indicated.

inhibitors also target other kinases, including RSK (15), and both have also been shown in some, but not all, circumstances to inhibit the activation of the ERK1/2 cascade (40). Two groups have reported the development or isolation of other potential MSK inhibitors. Four cheilanthane sesterterpenoids isolated from the marine sponge *Ircinia sp*. have been reported to inhibit MSK1 *in vitro*, although the specificity of these compounds against other AGC kinases has not been reported (41). Bamford *et al* have reported the synthesis of a novel series of imidazo(4,5-c)pyridines that were able to inhibit MSK1, and development of these lead compounds resulted in inhibitors with selectivity for MSK over GSK3 and RSK *in vitro* (42, 43). Both the specificity and the inhibition of MSKs by these compounds *in vivo* have not yet been reported.

5. MSK SUBSTRATES

MSKs have been shown to phosphorylate several proteins *in vivo* including CREB, ATF1, histone H3, HMGN1 and NFkappaB. Other possible substrates have been suggested for MSKs, including ER81 (44), ATF2 (45), 4EBP1 (46), Bad (47), Akt/PKB (48), STAT1 (49) and STAT3 (50), however these proteins are also phosphorylated by other kinases and definitive validation that they are *in vivo* MSK targets is lacking.

MSKs phosphorylate serine or threonine residues, and although it has not been possible to define a precise substrate recognition sequence for MSKs *in vitro*, there is a clear requirement for a cluster of basic residues immediately before the phosphorylation site (Figure 3). *In vitro*, many of the sites phosphorylated by MSK in protein substrates can also be phosphorylated by other AGC kinases, particularly RSK and PKA. For instance, *in vitro* both MSK and RSK phosphorylate nur77 at the same site, while CREB and LKB1 are phosphorylated by PKA, MSK and RSK at the same sites (7, 40, 51, 52). In cells, both MSK and RSK can be activated by similar signals, suggesting that there may be some redundancy for these kinases in the phosphorylation of substrates *in vivo*. In practice this does not seem to occur as RSK and MSK seem to act on distinct targets in the cell. For example, in cells both LKB1 and nur77 are phosphorylated by RSK and not MSK (40, 52), while CREB is a target for MSK and not for RSK (12).

5.1. CREB

CREB was the first *in vivo* substrate of MSKs to be identified. A role for MSK in CREB phosphorylation was first suggested from the *in vitro* screening of potential peptide substrates for MSK1 (7). This identified a peptide whose sequence corresponded to the Ser133 phosphorylation site in CREB as an excellent substrate for MSK1. Further work confirmed that the full length CREB protein was also a very good *in vitro* MSK substrate (7).

The proposal that MSK was an *in vivo* CREB kinase however was at first controversial. In cells, CREB is phosphorylated on Ser133 downstream of distinct signalling pathways in response to a variety signals. PKA was the first CREB kinase to be identified, and phosphorylates Ser133 in CREB in response to agents that elevate cyclic AMP. Ca^{2+} signalling has also been shown to promote CREB phosphorylation, most probably via one of the CaMK protein kinase family (reviewed in (53-55)). CREB is also phosphorylated on Ser133 in response to mitogens and cellular stress, and for these stimuli the MEK1/2 inhibitor PD90859 and p38 inhibitor SB203580 have been used to demonstrate a role for the ERK1/2 and p38 MAPK pathways respectively (7, 56-58). CREB is not however a direct target for MAPKs, and therefore must be phosphorylated by one of the downstream kinases. Initial reports, before MSKs were first cloned, suggested that RSK phosphorylated CREB downstream of ERK1/2 (51) while MK2 phosphorylated CREB downstream of p38 (57). The discovery that MSK1 was activated downstream of both ERK1/2 and p38 however meant that these findings have to be re-evaluated.

Downstream of p38, the use of kinase inhibitor Ro 318220 was used to distinguish MSKs and MK2. In UV-C stimulated HEK-293 cells, CREB phosphorylation requires the activity of the p38 but not ERK1/2 pathway. Under these conditions Ro 318220, which is a potent MSK inhibitor but does not affect MK2, was found to block UV-C induced CREB phosphorylation, strongly suggesting that MSK, and not MK2, phosphorylated CREB downstream of p38 (7). This finding was later confirmed using cells from knockout mice. In murine embryonic fibroblasts (MEF), anisomycin and UV-C induce CREB phosphorylation predominantly via the p38 pathway. CREB phosphorylation was found to be normal in anisomycin stimulated MEFs from MK2 mice (59). In contrast, a double knockout of both MSK1 and MSK2 abolished both UV-C and anisomycin induced CREB phosphorylation in MEF cells (12). Single knockouts of MSK1, and to a lesser extent MSK2, showed reduced CREB phosphorylation, suggesting that both MSK1 and MSK2 are able to phosphorylate CREB *in vivo* (12).

Downstream of ERK1/2 it was less easy to resolve which kinase phosphorylates CREB, as both RSKs and MSKs are inhibited by Ro 318220. The evidence that RSK phosphorylated CREB came from 3 main findings.

RSK was reported as the major mitogen induced CREB kinase that was isolated from cell extracts by a biochemical purification. RSK activity is however much more abundant in cells than either MSK1 or MSK2 activity, thus explaining why it, and not MSKs, were found by biochemical purification. This does not however indicate that RSK is the major *in vivo* kinase.

Secondly, dominant negative RSK2 was found to block CREB phosphorylation in cells (51). It is possible however that in these experiments the dominant negative RSK2 acts through an indirect mechanism rather than directly blocking phosphorylation of CREB by RSK. Relevant to this, it has been shown that dominant negative RSK can block the activation of MSK1, presumably by binding to active ERK1/2 and sequestering it away from MSK1 (60). The third piece of evidence came from cells isolated from patients with Coffin-Lowry-Syndrome (CLS), who are homozygous for a mutation that destroys RSK2 activity (61). EGF induces CREB phosphorylation via the ERK1/2 pathway, however in the CLS cells, which lack RSK2 activity, EGF failed to induce CREB phosphorylation (61). This result has however been questioned, as data from RSK2 knockout mice demonstrated that RSK2 was not required for CREB phosphorylation downstream of ERK1/2 following PDGF stimulation (62).

The most convincing evidence for MSK phosphorylation of CREB comes from knockout mice. MEF cells from MSK1/MSK2 knockouts were found to have greatly reduced CREB phosphorylation in response to both PMA and EGF, stimuli that act predominantly via the ERK1/2 pathways in MEF cells (12). PMA or EGF stimulation of embryonic stem (ES) cells and BDNF stimulation of cortical neurons also induces CREB phosphorylation via the ERK1/2 cascade. Again, for these cells and stimuli CREB phosphorylation was greatly reduced in cells from MSK knockout mice (60, 63). It should be noted that knockout of both MSK1 and MSK2 does not completely prevent the phosphorylation of CREB in response to mitogens and growth factors, indicating that another kinase is able to phosphorylate CREB in these circumstances. The kinase responsible for this residual phosphorylation has not been definitively identified, and it is also not clear if this is a normal physiological function of this kinase or a compensatory mechanism that occurs due to the lack of MSKs in the knockout cells.

A final piece of evidence that MSKs, and not RSK, are the predominant kinases that phosphorylate CREB downstream of ERK1/2 has come from a recently described RSK inhibitor Bi-D1870, a compound that does not inhibit MSK activity. Bi-D1870 did not significantly inhibit CREB phosphorylation in either PMA stimulated Rat-2 or EGF stimulated HEK293 cells (64). In the same experiments BI-D1870 did block the phosphorylation of the RSK substrates GSK3 and LKB1.

CREB is a member of a subfamily of b-zip transcription factors that also includes ATF1 and CREM. The Ser133 phosphorylation site in CREB is conserved in both ATF1 and CREM. Similar to CREB, phosphorylation of ATF1 on Ser63 (the analogous site to Ser133 in CREB) occurs in response to mitogens and cellular stress, and is also catalysed by MSK1 and MSK2 (12).

CREB binds to cyclic AMP response elements (CRE) in the promoters of many genes. In many cases this binding appears to be constitutive and is not regulated by mitogens or cellular stress. Phosphorylation of Ser133 is however required for the full transcriptional activity of CREB, as it creates a binding site allowing the recruitment of the coactivator proteins p300 or CBP. Thus CREB phosphorylation has been shown to regulate the transcription of a large number of genes, many of which are classical immediate early (IE) genes (reviewed in (53)). MSKs have been shown to be involved in the regulation of several CREB regulated IE genes, including c-fos (12, 23, 24), junB (12), nur77, nurr1, nor1 (19), mkp1 (60), Cyr61 (65), MUC5AC (21) and cox-2 (66, 67).

5.2. Chromatin associated proteins

Histone H3 is a component of the nucleosome, and consists of a globular domain that forms part of the core nucleosome structure, and an N-terminal tail that extends out of the nucleosome. As in histone H2 and H4, this N-terminal tail is the site of many post-translational modifications, including acetylation, methylation, ubiquitination and phosphorylation. This results in a huge number of possible combinations of modifications on the histone tails of an individual nucleosome. This has lead to the hypothesis that different combinations of histone tail modifications 'tag' regions of chromatin in a specific way, which could in turn affect processes such as the modification of chromatin structure, transcription and gene silencing. This is frequently referred to as the histone code, and has been extensively reviewed (68-71). The phosphorylation of H3 in response to mitogens or stress was first reported in 1991 (72). Based on the use of inhibitors such as PD98059 and SB203580, a role for the ERK1/2 and p38 cascades was demonstrated in H3 phosphorylation (73-75), while the use of H89 to inhibit MSKs suggested a role for MSK1 (73, 76). As with CREB phosphorylation, there was some initial controversy as to the roles of RSK and MSK in H3 phosphorylation (77, 78). The use of fibroblasts from MSK1/2 knockouts was again able to show that MSKs, and not RSK, were the major H3 kinases downstream of the ERK1/2 and p38 cascades (75, 77). Subsequently MSKs have been reported to phosphorylate histone H3 in a variety of other systems, including in neurons and during ES cell differentiation (79, 80).

In addition to Ser10, MSK was also found to phosphorylate a second site on H3, Ser28 (75). It should be noted that while both Ser10 and Ser28 in H3 are extensively phosphorylated during mitosis, this is independent of MSKs and is catalysed by Aurora kinases. In contrast, MSKs only phosphorylate a small proportion of the total cellular histone H3 in response to mitogens or stress. The spatial distribution of Ser10 and Ser28 phosphorylation is very tightly regulated in cells. *In vitro*, MSK1 will phosphorylate one histone H3 molecule on both Ser10 and Ser28. Surprisingly it has been shown that in

cells MSK phosphorylates either Ser10 or Ser28 but not both on individual nucleosomes, and that Ser10 and Ser28 phosphorylation do not colocalise in the nucleus (81, 82). The mechanism by which MSK is recruited to chromatin and directed to phosphorylate either Ser10 or Ser28 in H3 is not however known. The role of Ser28 phosphorylation in H3 is not yet clear; while Ser28 phosphorylation has been shown to occur in non-condensed chromatin, it is not clear which, if any, genes it is associated with (81). In contrast, using chromatin immunoprecipitation, Ser10 phosphorylation has been shown to occur at the promoters of several IE genes in mammalian cells, including c-fos, c-jun and c-myc, following either mitogenic stimulation or cellular stress (83). However while there is a clear correlation between Ser10 phosphorylation and transcriptionally active loci, the precise mechanism by which Ser10 phosphorylation could regulate transcription is not established. In yeast, it was suggested that H3 phosphorylation may affect the subsequent acetylation of H3. Yeast studies have also shown that mutation of Ser10 in H3 to alanine reduced the transcription of a subset of genes. This suggests that H3 phosphorylation can affect transcription, but that this effect is not universal and it is dependent on the promoter or chromatin context. In *Drosophila,* it has been suggested that the effect of H3 phosphorylation on transcriptional activation is dependent on promoter context (reviewed in (10)). In mammalian cells, H3 phosphorylation does not appear to affect the acetylation of H3, and it is likely that these modifications occur independently. It has not been easy to define a role of Ser10 by mutagenesis, as there are multiple copies of the H3 gene. While it is possible to block H3 phosphorylation by using MSK inhibitors or knockouts, the interpretation of these experiments with regards to gene transcription are complicated as the phosphorylation of other MSK substrates, including CREB, is also blocked. It is not easy to extrapolate from the genes regulated by H3 Ser10 phosphorylation in yeast to mammalian cells, as yeast lack an MSK homologue, and in yeast H3 phosphorylation is carried out by different kinases downstream of different pathways compared to mammalian cells.

An attractive explanation of how H3 phosphorylation may affect transcription is that it could modulate the recruitment of other proteins to chromatin. Specific binding domains for phosphorylated histone H3 tails have not yet been identified, however phosphorylation of histone H3 on either Ser10 or Ser28 does create a potential binding site for 14-3-3 proteins (84). 14-3-3 proteins are a family of proteins that bind to phospho-peptides with an optimal recognition sequence of R-S-X-pS-X-P or R-X-Y/F-X-pS-X-P (85). Although the phosphorylation sites in histone H3 do not conform to this consensus sequence, phospho-peptides corresponding to H3 Ser 10 or Ser28 do bind to purified 14-3-3 proteins *in vitro*. Furthermore anisomycin treatment of C3H 10T1/2 fibroblasts stimulates both H3 Ser10 phosphorylation and 14-3-3 recruitment to the c-fos and c-jun promoters (84). The function of 14-3-3 recruitment is unclear; however it may act to either displace transcriptional inhibitors or, as 14-3-3 proteins are dimmers with two phospho-peptide binding sites, it may allow recruitment of other phospho proteins.

Acetylated or methylated histones have been shown to bind to bromo or chomo domains respectively, allowing the recruitment of proteins containing these domains to chromatin. Methylation of Lys9 in histone H3 frequently correlates with transcriptional silencing, and creates a binding site for HP1. During mitosis it has been shown that phosphorylation of histone H3 on Ser10 promotes the dissociation of HP1 from chromatin. Recently, it has also been shown that the phosphorylation of H3 by MSK1 on the MMTV promoter can decrease the binding of HP1 to this promoter, thus providing a possible mechanism for how H3 phosphorylation may regulate transcription (86).

In addition to histone H3, MSKs also phosphorylate another chromatin associated protein, HMGN1 (also called HMG-14) (75). HMGN1 does not form part of the core nucleosome, however it binds to nucleosomes and thereby reduces chromatin compaction. In addition, HMGN1 binding can inhibit histone H3 phosphorylation in chromatin, most probably by reducing the access of the kinase to the chromatin fibres (87). Phosphorylation of HMGN1 by MSKs is proposed to transiently decrease the interaction of HMGN1 and nucleosomes, thus allowing access of MSK to the core histones (87).

5.3. NFkappaB

NFkappaB is known to regulate transcription in response to a diverse range of stimuli and has been implicated in many cellular processes. NFkappaB itself is a dimer of two of the NFkappaB proteins, RelA (p65), RelB, c-REL, p105/p50 and p100/p52 (for reviews see (88, 89)). In its inactive state, NFkappaB is held in the cytoplasm, and can be activated by two main mechanisms, referred to as the canonical and noncanonical pathways. In the canonical pathway, NFkappaB dimers in the cytoplasm are bound to an inhibitory IkappaB complex. In response to stimulation, IkappaB proteins are phosphorylated by the IKK complex. This phosphorylation promotes the degradation of IkappaB, allowing free NFkappaB dimers to translocate to the nucleus, where they are transcriptionally active. The noncanonical pathway acts on NFkappaB dimers containing a p100 subunit that are not complexed to IkappaB. This pathway requires the activation of IKKalpha, which directly phosphorylates p100 resulting in its proteolytic processing to give rise to p52. The p52 containing NFkappaB dimer is then able to translocate to the nucleus (for reviews see (88, 89)). In addition, NFkappaκB activity can also be modulated by a range of post-translational modifications, including the phosphorylation and acetylation of multiple residues (88, 89).

Ser276 in p65/RelA was originally identified as a site phosphorylated by a PKA catalytic subunit complexed to IKK (90). Subsequently it was reported that MSK1 could also phosphorylate this site in response to TNF in fibroblasts (91), and that this phosphorylation did not occur

in MSK1/2 knockout fibroblasts (92). The phosphorylation of Ser276 does not appear to regulate the nuclear entry of NFkappaB or its ability to bind its target sites in DNA. Ser276 phosphorylation is however thought to promote the recruitment of the coactivator p300/CBP, which in turn can acetylate both NFκB and histones at the NFkappaB bound promoters (92). Phosphorylation of other sites in p65/RelA is also reported to play a similar role in coactivator recruitment, so the exact physiological relevance of Ser276 phosphorylation is not clear. Reconstitution of p65/RelA null cells with either wild type or Ser276Ala mutant p65 has shown that while p65/RelA phosphorylation may affect the transcriptional activity of NFkappaB, this is very promoter specific. For instance, TNF-induced *ICAM-1* and *MIP2* transcription was not rescued by a Ser276Ala p65/RelA mutation while *MHC class I* and *IL-6* transcription was (93).

6. PHYSIOLOGICAL ROLES OF MSKS

One important consequence of activation of both ERK1/2 and p38 signalling is the transcriptional induction of many IE genes. While ERK1/2 and p38 can regulate IE genes via the direct phosphorylation of transcription factors, (including Ets domain transcription factors, MEF2 and components of the AP1 complex (2)) a proportion of these IE genes, such as *c-fos, mkp-1* and *nur77*, are also regulated by CREB (53). In cell culture systems, MSKs have been shown to play clear roles in the induction of CREB dependent IE genes downstream of ERK1/2 or p38. Knockout of MSKs might therefore be expected to show a severe phenotype, but surprisingly mouse knockouts that lack both MSK1 and MSK2 are viable, fertile and show no obvious developmental or welfare problems (12). Despite this, it has been shown that a number a cell types derived from these mice are deficient in the mitogen or stress induced phosphorylation of CREB, ATF1 and histone H3 (12, 60, 75, 94). This in turn results in reductions in the transcription of specific IE genes. The phenotype of MSK1/2 knockout mice is in contrast to that of the knockout of CREB, which results in perinatal lethality (95), or double knockout of both CREB and ATF1, that results in embryonic lethality (96). This difference is mostly likely explained by the fact that CREB and ATF1 are phosphorylated by a number of other kinases, such as PKA or CaMKs, downstream of distinct signalling pathways (53), and it is likely that these kinases are controlling the developmental functions of CREB. This however raises a question regarding the physiological roles of MSK. While much work is still required to fully answer these questions, some studies are starting to give some insights into these questions. In some circumstances MSKs may affect cell survival. For example, MSK activation has been shown to play a role in the apoptosis of hippocampal neurons following Mg^{2+} withdrawal (97) and in the Mn^{2+} induced apoptosis of B cells (98). In contrast knockout of MSK1 and 2 sensitises fibroblasts to arsenic trioxide induced death (26). The precise mechanism by which MSKs exert these effects is unknown. In addition it is now becoming apparent that MSKs may play specific roles in both immunity and neuronal function.

6.1. MSKs in immunity

6.1.1. T cell development

Both MAPK signalling and CREB are reported to play a role in T cell development, and this together with the finding that the T cell receptor (TCR) induces CREB phosphorylation via the ERK1/2 pathway suggests that MSKs may play a role in T cells. Consistent with this, it has recently been reported that both TCR and IL-2 induced CREB phosphorylation is greatly reduced in cells from MSK1/2 knockout mice (99). CREB knockout in mice was reported to result in a significantly decreased number of embryonic thymocytes and impaired foetal αβ T cell development (95). It is not clear however to what extent this phenotype was due to defects within the T cells or in problems with stromal support during T cell development. A combination of total ATF1 knockout and a T cell specific CREB knockout in mice did not block thymic T cell development, although a slightly reduced thymocyte number was observed. In addition a slower recovery in thymic cell number following sublethal irradiation was also reported in these mice (100). MSK1/2 knockout mice however were found to have normal thymocyte number and no defects in thymic CD4 / CD8 T cell development. The number of T cells in the spleen of MSK1/2 knockout mice was however slightly reduced, as was their potential to proliferate in response to stimulation via the TCR (99). The transcription of two TCR induced IE genes, *nur77* and *nor1*, has been previously linked to MSKs in other cell types (19). Both *nur77* and *nor1* are suggested to play a role in T cell apoptosis and negative selection in the thymus (reviewed in (101)). Analysis of the transcriptional induction of *nur77* and *nor1* downstream of the TCR in T cells showed that while the transcription of these genes was dependent on MAPK signalling, it was independent of MSKs (99). This was surprising given that MSK are required for the MAPK regulated transcription of these genes in fibroblasts, neurons and macrophages.

5.1.2) TLR signalling

MAPK signalling is critical for the action of the innate immune system. Cells in the innate immune system detect infection using specific receptors, which detect certain microbial or vial specific products, referred to as pathogen derived molecular patterns (PAMP). One group of receptors that are able detect PAMPs are the toll like receptors (TLRs) (reviewed in (102-104)). TLR signalling is well established to activate a number of intracellular signalling cascades including the ERK1/2, p38 and NFkappaB pathways (105). Activation of these cascades results in a variety of effects, including the induction of a range of cytokines and chemokines that coordinate the immune response. The p38 pathway in particular has attracted a significant amount of attention, as p38 inhibitors have been shown to reduce pro-inflammatory cytokine production, and have been effective in several animal models of inflammation (reviewed in (106-109)). Further interest in this pathway was stimulated by the finding that the p38 activated kinase MK2 regulates the production of TNF, and that MK2 knockouts are resistant to endotoxic shock (110). Activation of the ERK1/2 and p38 cascades would be expected to result in MSK activation, and consistent with this, LPS, which activates MAPK signalling

via TLR4, has been shown to activate MSK1 in macrophage cell lines (66, 111) and in primary macrophages (112). HP0175, another potential TLR4 agonist, has also been shown to activate MSK1 in a human monocyte/macrophage like cell line (105). MSK1 has also been shown to be activated downstream of TLR2 (67), and it is likely that other TLRs also activate MSKs although this has still to be investigated. The physiological roles of MSKs downstream of TLR signalling are still to be elucidated, however it is likely that MSKs will contribute to the regulation of transcription downstream of TLR signalling. For instance, MSKs have already been suggested to regulate the transcription of interleukin 6 (IL-6). In the THP-1 human monocyte cell line, siRNA knockdown of MSK1 was reported to inhibit IL-6 secretion in response to the *H. pylori* HP0175 protein, an agonist of TLR signalling (105), while TNF induced IL-6 transcription was shown to be reduced in MSK1/2 knockout fibroblasts (91). IL-6 transcription is regulated in part by NFkappaB, and in both cases MSK was proposed to regulate IL-6 production via the phosphorylation of NFkappaB on Ser276. It is not clear however if MSK contributes to IL-6 transcription in all circumstances. For instance, a p65/RelA Ser276Ala mutant has been reported to restore IL-6 transcription in p65/RelA deficient fibroblasts (93). Furthermore the transcription of IL-6 in response to LPS is not reduced in bone marrow derived macrophages from MSK1/2 knockout mice (SA, unpublished observations). MSKs have also been reported to regulate the transcription of cox-2 (also known as Ptgs2) in response to TLR signalling (66, 67). This regulation most probably occurs via the phosphorylation of CREB or ATF1 on the cox-2 promoter by MSKs. Cox-1 and Cox-2 are the rate limiting enzymes in the conversion of arachidonic acid to prostaglandin H2. Cox-1 is constitutively expressed where as Cox-2 is induced via a range of stimuli, including TLR agonists (reviewed in (113, 114)). Much of the prostaglandin synthesis in inflammation is attributed to Cox-2, and initially Cox-2 was thought of as pro-inflammatory gene. This concept was reinforced by the finding that some of the anti-inflammatory effects of aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) was due to their ability to inhibit Cox-1 and Cox-2 (113, 114). This however is unlikely to be the full story, as more recently it has become apparent that some of the metabolites of prostaglandin H2 are involved in promoting the resolution of inflammation (114). This also raises the interesting question of whether MSK activation in the innate immune system is on balance pro- or anti-inflammatory. Relevant to this mouse knockouts of another CREB dependent IE gene, DUSP1, have shown that DUSP1 is required to limit pro-inflammatory cytokine production downstream of TLR signaling (reviewed in (115, 116)). It will therefore be of interest to look at the regulation of DUSP1 by MSKs in the immune system. Further work will therefore be required to understand the role of MSKs in immunity.

It will also be of interest to determine if MSK is activated in autoimmune disorders. Only two studies have looked at this to date. These have shown that both MSK1 and MSK2 activity is increased in lesional psoriatic skin relative to normal controls (117, 118).

6.2. MSKs and behaviour

It has been well established that both ERK1/2 and CREB play important roles in IE gene transcription in neurons, and as a result affect the differentiation and survival of neurons as well as neuronal specific processes such as long term potentiation (LTP) and memory (reviewed in (119-122)). While this is suggestive of important roles for MSKs in neurons, it must also be stressed that many of the neuronal functions of ERK1/2 are independent of CREB phosphorylation, and that CREB itself is a target of several kinase pathways in neurons.

In primary cortical neuron cultures, MSK1 has been shown to be activated in response to neurotrophins via the ERK1/2 cascade (60). In this system MSKs were required for BDNF and NT3 stimulated CREB (60) and histone H3 (SA, unpublished) phosphorylation. In contrast to other cells, MSK2 does not appear to play a major role in cortical neurons. A single knockout of MSK1 was found to block neurotrophin induced CREB phosphorylation to the same extent as seen in MSK1/2 double knockouts, while single knockouts of MSK2 had no effect on neurotrophin induced CREB phosphorylation (60). This was in marked contrast to other cell types, such as macrophages and fibroblasts, where single knockout of either MSK1 or MSK2 could only partially block CREB phosphorylation, and a double knockout of both MSK1 and MSK2 was required to fully inhibit CREB phosphorylation (12). Presumably because of the lack of CREB phosphorylation, knockout of MSK1 and 2 also reduces the BDNF induced transcription of the CREB dependent IE genes *c-fos*, *nurr1* and *mkp-1* in cortical neurons (60). MSK1 has also been shown to be activated in the striatum by cocaine (94) and in the visual cortex suprachiasmatic nucleus by light (30, 123). As these stimuli also induce CREB and histone H3 phosphorylation in these brain regions, it is likely MSK may be responsible for these phosphorylations, and could therefore contribute to the behavioural responses induced by these stimuli.

One area in which ERK1/2 and CREB have attracted much research is in the molecular mechanisms that underlie memory, and in LTP, a form of synaptic plasticity (reviewed in (120, 122, 124)). CREB has been linked in several studies to the formation of LTP and the formation of long term memory (reviewed in (122, 124)). Initially, studies in both *Aplysia* and *Drosophila* both indicated an important role for cAMP signalling and CREB in these processes (122). Work using transgenic mice however has been much harder to interpret. A role for cAMP signalling in hippocampal dependent spatial memory as well as hippocampal LTP was found using both transgenic mice overexpressing a PKA inhibitor and mice with a targeted mutation in type 1 anenylate cyclase (125). As cAMP signalling lies upstream of CREB, it seemed reasonable to assume that CREB may be involved in hippocampal dependent memory. Consistent with this it has been reported that both hippocampal dependent tasks and LTP inducing stimuli result in both CREB phosphorylation and induction of CRE dependent IE genes. The results from CREB transgenic mice looking at hippocampal LTP and memory have however been less conclusive. In general,

techniques that would target both CREB as well as the related proteins CREM and ATF1, such as transgenic expression of a dominant negative form of CREB, support a role for CREB in memory (126). Studies on CREB knockout mice have however failed to see a consistent defect in spatial memory or hippocampal LTP (127). One explanation for this could be that in CREB knockouts CREM can be upregulated in neurons and may compensate for its function. Analysis of CREB/CREM double knockouts would therefore be desirable, however these mice undergo severe neurodegeneration making this analysis difficult (128).

While in many cell types cAMP activates PKA to phosphorylate CREB, in neurons the situation is less clear, as in these cells elevated cAMP levels and PKA activation can also lead to ERK1/2 activation (129). Consistent with this, MSK1 has been shown to be activated by ERK1/2 in the hippocampus in response to a fear conditioning stimulus in mice, and that this does not occur in adenylate cyclase knockout mice (130). In addition to CREB phosphorylation, histone H3 phosphorylation has also been shown to occur in neurons (123, 131, 132), and it has been suggested that this may act as an epigenetic mark during LTP and memory formation (121). Fear conditioning stimuli lead to increases in both CREB and histone H3 phosphorylation in the hippocampus, however these phosphorylations are prevented by the knockout of MSK1 (133). Together these findings would suggest a role for MSK in LTP, however the effect of MSK1 knockout on LTP has not been reported. MSK1 knockouts have however been found to have reduced responses in fear conditioning, passive avoidance and water maze tests, all of which require hippocampal long term memory (133).

MSKs have also been shown to play a role in the response to cocaine in mice. MSK1 knockout prevents the phosphorylation of both CREB and histone H3 in the striatum following cocaine administration (94). Place preference tests determine if mice prefer a chamber where they have previously been given a substance over one where they were not. In place preference tests using low doses of cocaine during training, MSK1 knockout resulted in an increased preference compared to wild type mice for the chamber where cocaine was previously administered. This effect was not however observed when high doses of cocaine were used. Locomotor sensitization, which measured the increased activity of mice following repeated cocaine injections, was significantly decreased by knockout of MSK1 (94). While this is suggestive for a role of MSK1 in addiction, more work however will be needed to determine if MSK1 inhibition would promote or block addiction in human drug use.

7. PERSPECTIVES

Since their discovery in 1998, it has been established that MSK1 and MSK2 act downstream of ERK1/2 and p38 MAPK signaling pathways in a variety of cellular models. The main role of MSKs appears to be in the regulation of IE genes, due to their ability to phosphorylate the transcription factors CREB, ATF1 and NFkappaB as well as the chromatin proteins histone H3 and HMGN1. MSKs are not essential for mammalian development, and mouse knockouts do not exhibit an obvious phenotype under normal conditions. Despite this, it is becoming apparent that MSKs play important roles in both neurons and immune cells, however much more work is required to understand the physiological roles of MSK in these systems.

8. ACKNOWLEDGEMENTS

JSCA is funded by grants from the MRC, Arthritis Research Council, EU and Wellcome Trust. Due to limitations of space, it was not always possible to cite all of the primary research papers and I appologise to those whose work was not cited for this reason. I also thank John Rouse for the critical reading of the manuscript.

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Key Words: MSK1, MSK2, CREB, MAPK, ERK, P38, Histone H3, NfkappaB, Review

Send correspondence to: Dr Simon Arthur, MRC Protein Phosphorylation Unit, College of Life Sciences, University of Dundee, Dundee, DD1 5EH, UK, Tel: 01382384003, Fax: 01382223778, E-mail: j.s.c.arthur@dundee.ac.uk

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