Biochemical and Biophysical Research Communications 371 (2008) 1–4

Contents lists available at ScienceDirect

Biochemical and Biophysical Research Communications

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

Mini Review

MAP kinase: It's been longer than fifteen minutes

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ARTICLE INFO

Article history:
Received 1 April 2008
Available online 10 April 2008

Keywords:
MAP kinase
Cell cycle
MEK1
MEK2
ERK1
ERK2

ABSTRACT

The review highlights evidence for different functions in the cell cycle of the two MAP kinase kinases, MEK1 and MEK2, and the two MAP kinases, ERK1 and ERK2. Functional differences may explain why instances of cell cycle arrest can be MEK1 or MEK2 dependent.

A review from 1992 was entitled, "ERKs: their fifteen minutes has arrived [1]." The title notes the short attention span in life sciences for molecules. Attention to MAP kinase has been undiminished for longer than the figurative 15 min. Interest continues because MAP kinases are required for adaptation to so many cellular and developmental cues [2–5]. This large literature, currently over 40,000 papers and nearly 3000 reviews, is daunting. MAP kinases are used as convenient markers for cellular processes because phospho-specific antibodies easily detect their dual phosphorylation in a TXY motif. The glut of 'MAPK as marker' papers obscures the fact that much remains to be investigated and clarified in these signaling networks [6]. My topic here is focused, and my discussion is not comprehensive. I recall attention to different roles of MEK1 and MEK2 and ERK1 and ERK2 in the cell cycle.

A canonical MAP kinase pathway consists of a MAPKKK, a MAPKK (or MEK), a MAPK, and frequently a MAPKAP kinase. In the ERK signaling networks, the MAPKKKs are Raf-1, B-Raf, A-Raf, c-Mos, MEKK1, and Tpl2 [3]. These may activate MEK1 or MEK2. MEK1 or MEK2 may activate ERK1 or ERK2. At endogenous levels of expression, there is evidence for preferential coupling, which may depend on the MAPKKK or adapter proteins in addition to differences in their direct interactions. Raf-1 complexes preferentially with MEK1 [7], and Raf-1 and MEK1 can form a complex [8]. Isolation of Raf-1 complexes that associate with MEKK1 and can be co-purified suggests that Raf-1 complexes preferentially contain MEK1 and ERK2 [9].

MAP kinases in cell cycle progression

The name mitogen-activated protein kinase was chosen [10] because Cooper and Hunter defined tyrosine phosphorylation of $p42^{MAPK}$ as the most prominent response to mitogens in fibroblast cell lines [11,12]. $p44^{MAPK}$/ERK1 was also identified as tyrosine phosphorylated in response to extracellular stimuli [13]. ERK2/$p42^{MAPK}$ (or ERK1/$p44^{MAPK}$) positively regulates cyclin D1 transcription and destabilizes $p27^{Kip}$ [14] to promote entry into the cell cycle. To halt the cell cycle, p38α MAPK inhibits cyclin D1 transcription [15] and destabilizes cyclin D1 [16]. Both Jun kinase and p38α stabilize CDK inhibitor $p21^{Cip1}$ [17].

Although MAP kinase ERK2 and/or ERK1 can positively regulate G1 progression in cell lines [4], in other contexts activation of PD98059-sensitive pathways can halt G1. For example, treatment of MCF7 cells with phorbol ester induces cell cycle arrest in G1 that is prevented by the MEK inhibitor PD98059 [18]. Hepatocyte growth factor induces cell cycle arrest of HepG2 cells, likewise dependent on PD98059-sensitive pathways [19]. Observations of MEK dependent cell cycle arrest are not limited to cancer cells. Cell cycle exit caused by v-Raf in IMR-90 fibroblasts is blocked by PD98059 [20]. PD98059 inhibits MEK1, MEK2, and MEK5 [21].

Oncogenic v-Ras causes cell cycle exit and induction of p53 and CDK inhibitor $p16^{Ink4}$ in primary cells [22]. Cell cycle arrest by v-Ras in primary fibroblasts mimics senescence in primary fibroblasts, the state of permanent growth arrest provoked by effects of cumulative cell divisions. These findings indicate an ERK halts the cell cycle in contrast to being required for G1 progression. An explanation for these opposite roles of MAP kinase is outstanding and still important. The residual controls for MAP kinase left in

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doi:10.1016/j.bbrc.2008.04.002

mesenchymal cells for control of the cell cycle may be different from epithelial cells. In small cell cancer of the lung, mutations inactivate Raf-1 and reintroduction of active Raf-1 inhibits growth and causes differentiation [23]. This has potential because a Raf-1 activator (ZM336372) inhibits carcinoid tumors [24].

Although v-Ras-induced senescence is blocked by PD98059 and mimicked by active MEK1-EE, how the ERK MAP kinases immediately downstream are involved is unclear. Wang et al. [25] provided evidence that cell cycle exit due to either v-Ras or MEK1-EE was due to a secondary activation of p38α because either inducer of senescence (v-Ras or MEK1-EE) was blocked by p38α inhibitor SB203580, and was mimicked by constitutively active MEK3 or MEK6 [25].

In different reports, arrest required activation of a different tumor suppressor: $p19^{Arf}$ [26,27]; $p16^{Ink4}$ [20,22,28,29]; or $p21^{Cip1}$ [30,31]. The complexity arises in part because these CDK inhibitors/tumor suppressors are upregulated and downregulated during normal cell cycles as well as in response to stress and checkpoint activations (see [32]).

Different functions of MEK1 and MEK2

There is evidence for different roles of the MEK1 and MEK2 in control of the mammalian cell cycle. Inhibition of both MEK1 and MEK2 in CCL39 fibroblasts (an immortalized, serum-dependent hamster line) with PD184352, specific for MEK1 and MEK2, arrests cells in G1 [33], indicating a requirement for MEK1 and/or MEK2 for G1 progression. Treatment of synchronized NIH3T3 cells in S-Phase with PD98059 causes arrest at G2 [34], indicating MEK1 and/or MEK2 (or MEK5) can be required for G2 progression and not just G1 to S.

The phenotypes for loss of MEK1 versus loss of MEK2 have been studied in HCT116 cells (a colon cancer line with WT p53) [35]. Silencing of MEK1 causes sustained $p21^{Cip1}$ induction and G1 arrest despite accumulation of cyclin D and arrest was accompanied by increased MEK2 and ERK activity. Sustained ERK activation is necessary for induction of cyclin D, but sustained $p21^{Cip1}$ induction in G1 causes senescence (see Ref. [36]). Silencing of MEK1 may have a compensatory response that involves MEK2.

Indeed, additional evidence points to MEK2 having non-overlapping functions with MEK1. Silencing of MEK2 in HCT116 cells caused a G2/M delay, growth inhibition, and centrosome amplification [35]. A G2/M function for MEK2 is indicated by ability of dominant-negative MEK2, but not dominant-negative MEK1, to inhibit arrest in G2/M after ionizing radiation [37].

The Erikson lab studied cell cycle phenotypes after MEK1 or MEK2 silencing [38]. Okadaic acid bypasses the arrest of FT210 (Ts) cells at G2, produced by inactivation of the cdc2 (Ts) allele at 39 °C, by activating MEK and Polo-like kinase 1 (Plk1). PD98059 blocked both activations, suggesting MEK1 or MEK2 was upstream of Plk1. Active MEK also co-localized with Plk1 [38]. Since specific silencing of MEK2 caused centrosome amplification [35], and since Plk1 is a key regulator of centrosomes [39], these findings taken together suggest a G2/M specific function of MEK2. Silencing MEK1 but not MEK2 caused an earlier arrest in G2 (4 N content of DNA). Thus, it is important to find out what the phenotype of silencing MEK2 really is. HCT116 cells are WT for p53 whereas Hela cells are mutant for p53, as one potential factor.

Neither MEK gene alone is essential to transit a cell cycle, suggesting compensation. MEK2(−,−) mice live [40], and MEK1(−,−) cells grow. MEK1(−,−) embryos die with placental defects, and the MEK1(−,−) MEFs have a specific defect in cell migration in response to exposure to fibronectin [41]. MEK1 and MEK2 can be differentially activated [42], with serum potently activating MEK1 not MEK2 [42], consistent with differential function for MEK1 in G1 progression.

Specific regulation of MEK1 by phosphorylation

MEK1 may be phosphorylated but unable to signal to MAPK during a normal mitosis. Proline-rich inserts in MEK1 and MEK2 contain different potential phosphorylation sites [43] (Fig. 1). CDK2/cyclin B inactivates MEK1, but not MEK2, by phosphorylation of T292 and/or T286 in the insert [44]. The negative site is T286 by ability of a T286A mutant to rescue MAP kinase activation in mitosis [45]. CDK5/cyclin p35 also phosphorylates T286 to inactivate MEK1 [46]. MEK1 is phosphorylated at T292 and T386 sites, with kinetics consistent with ERK feedback [47]. Rac-PAK signaling at S298 is required for integrin-dependent ERK activation by MEK1 [48], making S298 a positive site. Rac-PAK signaling promotes specifically MEK1-ERK2 coupling.

ERK1 and ERK2: are there non-overlapping functions?

ERK1 and ERK2 are ~85% identical protein kinases that have mostly overlapping, and possibly some non-overlapping functions. Silencing ERK2 inhibits G1 progression in NIH3T3 cells [49]. ERK2 was more abundant than ERK1 [49]. When ERK2 was reduced by siRNA, a striking increase in ERK1 activation was observed [49]. When ERK2 levels were sufficiently reduced, G1 progression became partially dependent on ERK1, supporting a shared function of ERK2 and ERK1 in G1 progression [49]. In contrast, the non-overlapping functions of ERK1 and ERK2 are the most poorly supported. Do they even exist?

ERK1 knockout mice were viable [50], whereas knockout mice for ERK2 were embryonic lethal [51,52]. Trophoblast cells fail to proliferate in ERK2(−,−) embryos, resulting in early lethality, at ~E6.5. No ERK2(−,−) MEFs have been isolated despite attempts (M. Ogata).

ERK1(−,−)/ERK2(+,−) MEFs with one ERK2 allele have been isolated and proliferate in culture (S. Meloche). An experiment to place ERK1 under control of the ERK2 promoter might tell us if ERK1 can do everything ERK2 can do.

Defects in ERK1 versus ERK2 activation in senescence suggest divergent functions. Serum stimulates tyrosine phosphorylation of ERK2 in young MRC-5 cells, but not in senescent MRC-5 cells [53]. These are older observations that require reexamination. Senescent cells starved for 48h in low serum maintain tyrosine

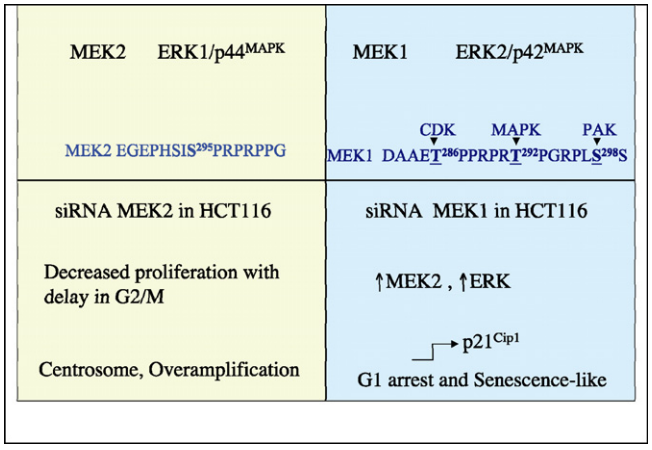

Fig. 1. MEK1 and MEK2 may have distinct cell cycle phenotypes. (The phenotypes reported by Ussar and Voss [35] are summarized in the lower panels.) Preferential coupling of MEK2 to ERK1, and MEK1 to ERK2 for some non-overlapping function is a pure speculation, from the correlation that MEK1 and ERK2 are both essential in conventional gene knockouts in mice. The phosphorylations in the proline-rich insert are shown for MEK1. T286 is an inhibitory site. S298 is a positive site, and integrates with integrin signaling (see text).

phosphorylation of ERK1 but not ERK2 [53], weakly suggesting that ERK1 is responsible for arrest in senescence. Progression to S-phase is stimulated by c-Myc. ERK2 expression but not ERK1 expression stimulates a c-Myc reporter [54], and ERK2 expression induces phosphorylation of c-Myc at Ser62 [55].

Vantagiatto et al. reported that ERK1(−,−) fibroblasts have more rapid growth that is lowered by expression of ERK1 [56]. These findings differ from the conclusions of a recent study of the overlapping function of ERK1 and ERK2 in G1 progression in different cells [49]. However, what should not be ignored were the large differences reported for ERK1 versus ERK2 overexpression on v-Ras induced tumors in explant experiments in nude mice. Specifically, ERK2 overexpression enhanced size of v-Ras tumors, whereas ERK1 overexpression did the opposite. These surprising findings merit independent study. There are differences in expression of ERK1 versus ERK2 in some tumors. For example, ERK1 is highly expressed in MCF-7 breast cancer cells in comparison to more aggressive ZR75, HS578T, and MDA-MB231 lines, whereas ERK2 is higher in a subset of aggressive lines in comparison to MCF-7 [57].

Other reports of ERK1 versus ERK2 differences

Activity of the transcription factor C/EBP$^{\beta}$ is regulated in G1 progression [58]. ERK2 but not ERK1 phosphorylated C/EBP$^{\beta}$ [59], and dominant-negative ERK2 but not dominant-negative ERK1 blocked mammalian 2-hybrid interaction of SRF and C/EBP$^{\beta}$ and this interaction requires the ERK2 site of phosphorylation in C/EBP$^{\beta}$ [59]. ERK1, but not ERK2, expression stimulates an ELK1 reporter [54]. Dominant-negative ERK1 but not dominant-negative ERK2 inhibits c-fos reporter and focus formation [60]. ERK2, but not ERK1, is required for proliferation and differentiation of myoblasts [61]. Loss of ERK1, but not ERK2, causes multinucleated cells [61].

Overexpression of Hsp25 induced p21^{Cip1} in L929 cells and caused radiation resistance. Resistance was suppressed by overexpression of ERK2 but not ERK1 [62]. Atrovastatin induced p27^{Kip1} and halted the cell cycle of T cells in G1. This correlated with a sustained increase in ERK1 activity not ERK2 activity [63] . ERK1 was found associated with alpha (v) beta (3) integrin after PDGF treatment, and dominant-negative ERK1 but not ERK2 reduced cell spreading on vitronectin [64]. Spreading on fibronectin was not affected.

Conclusion

The literature strongly supports different roles of MEK1 and MEK2 in regulation of mammalian cell cycles. Functional differences between ERK1 and ERK2 are controversial, but as I have attempted to do here, there are reports of differences. Why do some genomes maintain ERK1 and ERK2 but some only one ERK? *Ciona intestinalis* contains one MEK and one ERK. Are the retained MEK and ERK more similar to MEK1 and ERK2? A study of these points is pending (P. Lenormand). The practice of writing MEK1/MEK2 and ERK1/ERK2 may discourage discovery of differences, which may require modifications of experiment. The same is true for the other closely related MEKs and MAPKs in p38 and Jun kinase networks. Distinguishing functions of closely related proteins is not easy, and a field's attention span—too short.

Acknowledgments

T.W.S thanks Phillipe Lenormand, Christian Sardet, Jacques Pouysségur, Gilles L'Allemain, and Gilles Pagès for stimulating discussions and hospitality (even a fine Bandol) during visits to the Centre de Biochimie-CNRS Nice in and to the Station Zoologique-CNRS, Observatoire Océanologique in Villefranche in March, 2008.

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