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MINI-REVIEW

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Control of MAP kinase signaling to the nucleus

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Abstract MAP kinase (MAPK) signaling is among central signaling pathways that regulate cell proliferation, cell differentiation and apoptosis. As MAPK should transmit extracellular signals to proper regions or compartments in cells, controlling subcellular localization of MAPK is important for regulating fidelity and specificity of MAPK signaling. The ERK1/2-type of MAPK is the best characterized member of the MAPK family. In response to extracellular stimulus, ERK1/2 translocates from the cytoplasm to the nucleus by passing through the nuclear pore by several independent mechanisms. Sef (similar expression to *fgf* genes), a transmembrane protein, has been shown to be a regulator of subcellular distribution of ERK1/2. Sef binds to activated MEK1/2, the specific activator of ERK1/2, and tethers the activated MEK1/2/activated ERK1/2 complex to the Golgi apparatus and the plasma membrane. Thus, Sef blocks ERK1/2 signaling to the nucleus and allows signaling to the cytoplasm. Here we review recent findings on spatial regulation of MAPK, especially on nucleocytoplasmic trafficking of ERK1/2.

Introduction

The MAP kinase (MAPK) pathway is a highly conserved pathway involved in diverse cellular functions, including cell proliferation, cell differentiation and apoptosis. A wide variety of extracellular stimuli, such as growth factors and environmental stresses, induce sequential phosphorylation and activation of three protein kinases, MAP kinase kinase kinase (MAPKKK), MAP kinase kinase (MAPKK) and MAPK. MAPK is a serine/threonine kinase activated by MAPKK via phosphorylation on both threonine and tyrosine residues in the TXY sequence (Sturgill and Wu 1991; Ahn et al. 1992; Nishida and Gotoh 1993; Waskiewicz and Cooper 1995; Cobb and Goldsmith 1995). The MAPK family consists of four members, ERK1/2 (also known as classical MAPK), JNK/SAPK, p38 and ERK5/BMK1. Each molecule is activated by distinct pathways and transmits signals either independently or coordinately (Robinson and Cobb 1997; Davis 2000; Chang and Karin 2001). MAPK plays an important role in transmitting the signals from receptors on cell membrane to cytoplasmic targets such as cytoskeleton and downstream kinases and nuclear targets such as transcription factors. Thus, regulation of the subcellular localization of MAPK is important for controlling MAPK signaling.

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Regulatory mechanisms of ERK1/2 nuclear translocation

Regulatory mechanisms of subcellular distribution of the ERK1/2-type MAPK have been elucidated extensively. In quiescent cells, ERK1/2 is largely cytoplasmic and translocates to the nucleus upon stimulation. ERK1/2 does not have an authentic signal sequence for nuclear import (NLS) or nuclear export (NES). As ERK1/2 is small enough to enter the nuclear pore through passive diffusion (ERK1, 44 kDa; ERK2, 42 kDa), it is thought that there are anchor proteins which tether ERK1/2 in the cytoplasm. MEK1/2, an upstream kinase of ERK1/2, localizes to the cytoplasm because of its NES sequence in its N-terminal region (Fukuda et al. 1996). The binding of ERK1/2 to MEK1/2, which forms an ERK/MEK heterodimer, results in the cytoplasmic retention of ERK1/2, and nuclear translocation of ERK1/2 is accompanied by the dissociation of ERK1/2/MEK1/2 complex. Phosphorylation of ERK1/2 by MEK 1/2 is necessary and sufficient for the dissociation of ERK 1/2/MEK1/2 complex (Fukuda et al. 1997).

There are three independent mechanisms for nuclear translocation of ERK1/2; passive diffusion of a monomer,

active transport of a dimer, and importin-independent transport (Fig. 1). Phosphorylated ERK2 forms a homodimer with phosphorylated or unphosphorylated ERK2. Moreover, disruption of dimerization by mutagenesis of ERK2 reduces its ability to accumulate in the nucleus, indicating that dimerization is important for its translocation to the nucleus (Khokhlatchev et al. 1998). Importin-β and importin-7 were reported to be the components of this active transport machinery (Lorenzen et al. 2001). These studies suggest that dimerized ERK2 enters the nuclear pore by active transport. On the other hand, a dimerization-deficient mutant of ERK2 is still able to translocate to the nucleus, and its translocation is inhibited when this mutant protein is fused to β-galactosidase to make ERK2 too large (~160 kDa) to enter the nucleus by passive diffusion (Adachi et al. 1999). Moreover, neither wheat germ agglutinin (WGA) nor RanQ69L blocks completely the nuclear entry of ERK2, suggesting that monomeric ERK2 is able to translocate to the nucleus by passive diffusion. Recent reports showed the third pathway to the nucleus. GFP-fused ERK2, which is too large to pass through the nuclear pore by passive diffusion, is imported into the nucleus by a nuclear pore complex (NPC)-mediated, but cytosol- or ATP-independent, mechanism. ERK2 directly interacts with nucleoporin NUP214/CAN and NUP153, protein subunits of the NPC (Matsubayashi et al. 2001; Whitehurst et al. 2002). These results suggest that ERK1/2 passes through the nuclear pore by directly interacting with the NPC. Although it is unclear whether these three mechanisms are equally important in nuclear translocation of ERK1/2, active transport does not appear to be a major mechanism for nuclear import of ERK1/2, as a recent study with live cell imaging has shown that the movement of ERK1/2 into the nucleus upon stimulation can be explained for the most part by energy-independent mechanisms (Burack and Shaw 2005).

It has been shown that nuclear accumulation of ERK1/2 is regulated by nuclear anchoring proteins. The nuclear anchoring proteins are shown to be short-lived proteins, whose synthesis are regulated by the ERK1/2 pathway (Lenormand et al. 1998). Recently, DUSP5 (hVH-3/B23), an inducible nuclear phosphatase, has been proposed as a candidate for the inducible nuclear anchor for ERK1/2 (Mandl et al. 2005).

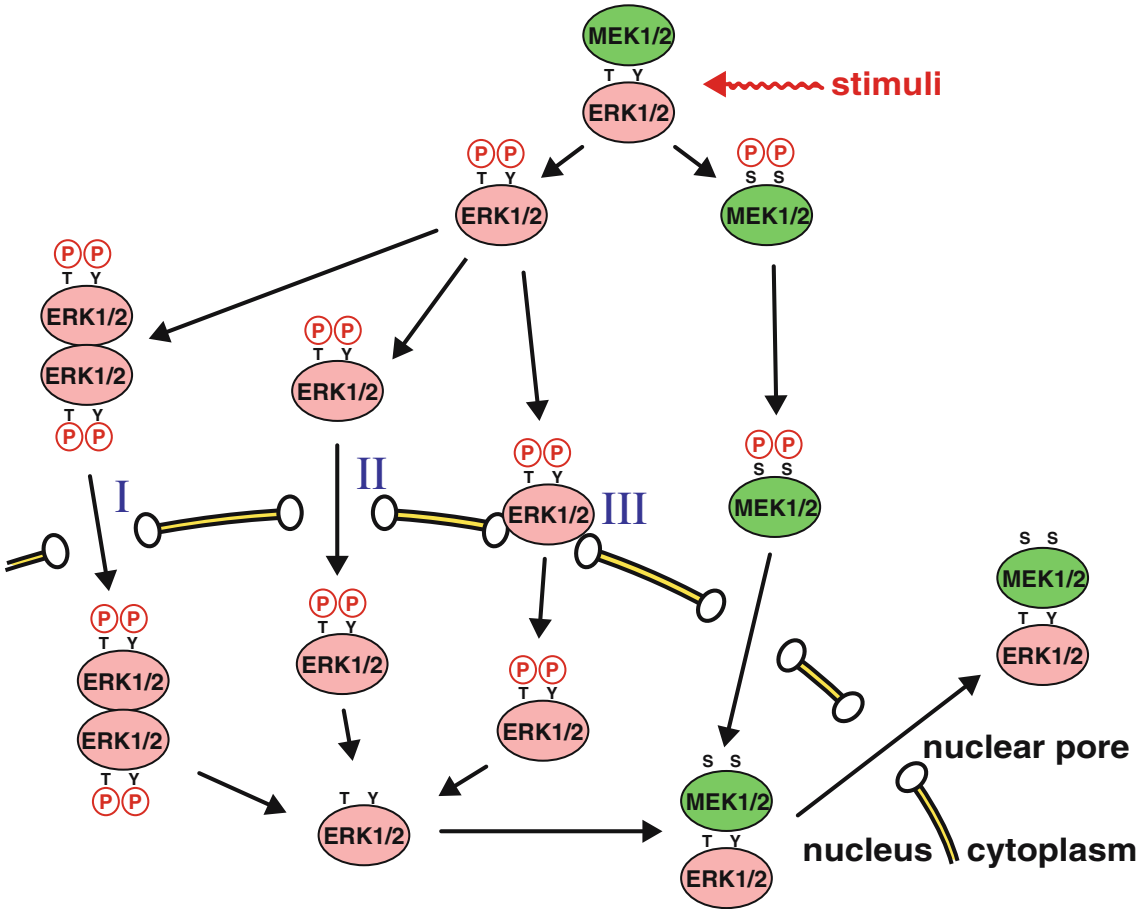

Fig. 1 Regulatory mechanisms of nuclear translocation of ERK1/2. In unstimulated conditions, ERK1/2 is bound to MEK1/2 and localizes in the cytoplasm because MEK1/2 has an NES. Upon stimulation, ERK1/2 dissociates from MEK1/2 and translocates to the nucleus by the use of three distinct mechanisms. I, ERK1/2 dimerizes and is actively transported to the nucleus; II, ERK1/2 passively diffuses into the nucleus; III, ERK1/2 passes through the nuclear pore by directly interacting with the NPC. Then, ERK1/2 is dephosphorylated and actively exported from the nucleus. MEK1/2 shuttles between the nucleus and the cytoplasm, and is able to carry ERK1/2 out to the cytoplasm

The nuclear accumulation of ERK1/2 is transient and ERK1/2 must relocalize to the cytoplasm to prepare for the next stimulation. Nuclear export of ERK1/2 involves a MEK1/2-dependent, active transport mechanism (Adachi et al. 2000). That is, MEK1/2 is shuttling between the cytoplasm and the nucleus, and carries ERK1/2 out to the cytoplasm by using the NES activity.

Sef regulates spatial direction of ERK1/2 signaling

While ERK1/2 phosphorylates and activates several nuclear targets including transcription factors, part of activated ERK1/2 localizes to the cytoplasm and phosphorylates cytoplasmic targets. Thus, the regulation of the spatial direction of ERK1/2 signaling is essential. Recently, it has been shown that Sef (similar expression to *fgf* genes) plays a pivotal role in regulation of spatial control of ERK1/2 signaling.

Sef, a putative transmembrane protein, was originally identified in zebrafish as an inhibitor of Ras/MAPK signaling (Futhauer et al. 2002; Tsang et al. 2002). Sef has been identified in other vertebrates and thought to be a conserved inhibitor of Ras/MAPK signaling (Furthauer et al. 2002; Tsang et al. 2002; Niehrs and Meinharbt 2002). Sef contains a predicted signal peptide, a transmembrane domain, an interleukin 17 (IL-17) receptor-like domain and a putative tyrosine phosphorylation site. Vertebrate Sef is expressed in highly restricted patterns in early stages of embryos, and its expression pattern is similar to the expression pattern of *fgf* genes, such as *fgf3*, *fgf8* and *fgf17*, and *sprouty* members, such as *sprouty2* and *sprouty4* (Tsang et al. 2002; Furthauer et al. 2002; Lin et al. 2002; Kawakami et al. 2003). Several reports indicate that Sef is induced downstream of Ras/MAPK signaling and acts as a negative regulator for Ras/MAPK signaling. However, there are contradicting reports concerning the action point of Sef. Several reports indicate that Sef acts downstream of, or at, MEK1/2 and inhibits phosphorylation of ERK1/2 (Futhauer et al. 2002; Yang et al. 2003; Preger et al. 2004). In contrast, other reports argue that Sef acts upstream of Ras by binding to FGF receptor (Kovalenko et al. 2003; Xiong et al. 2003).

Most recently, Torii et al. (2004) have shown that Sef acts as a spatial regulator for Ras/MAPK signaling by specifically inhibiting ERK1/2 nuclear translocation without inhibiting its activity in the cytoplasm (see Fig. 2). Reporter assays measuring the transcription activity of Elk1, a nuclear target of ERK1/2, have shown that Sef inhibits Ras/MAPK signaling downstream of, or at, MEK 1/2. In addition, Sef is shown to bind to the MEK1/2/ERK1/2 complex. Rather surprisingly, the binding of Sef to the MEK1/2/ERK1/2 complex does not affect the phosphorylation or the kinase activity of ERK1/2. Moreover, immunofluorescence experiments have shown that Sef colocalizes with both activated ERK1/2 and activated MEK1/2 mainly on the Golgi apparatus and partly in the plasma membrane in stimulated cell. Notably, Sef blocks active MEK1/2-induced dissociation of the MEK1/2/ERK 1/2 complex and thus inhibits ERK1/2 nuclear translocation. Consequently, Sef inhibits phosphorylation and ac tivation of nuclear ERK1/2 substrates without suppressing

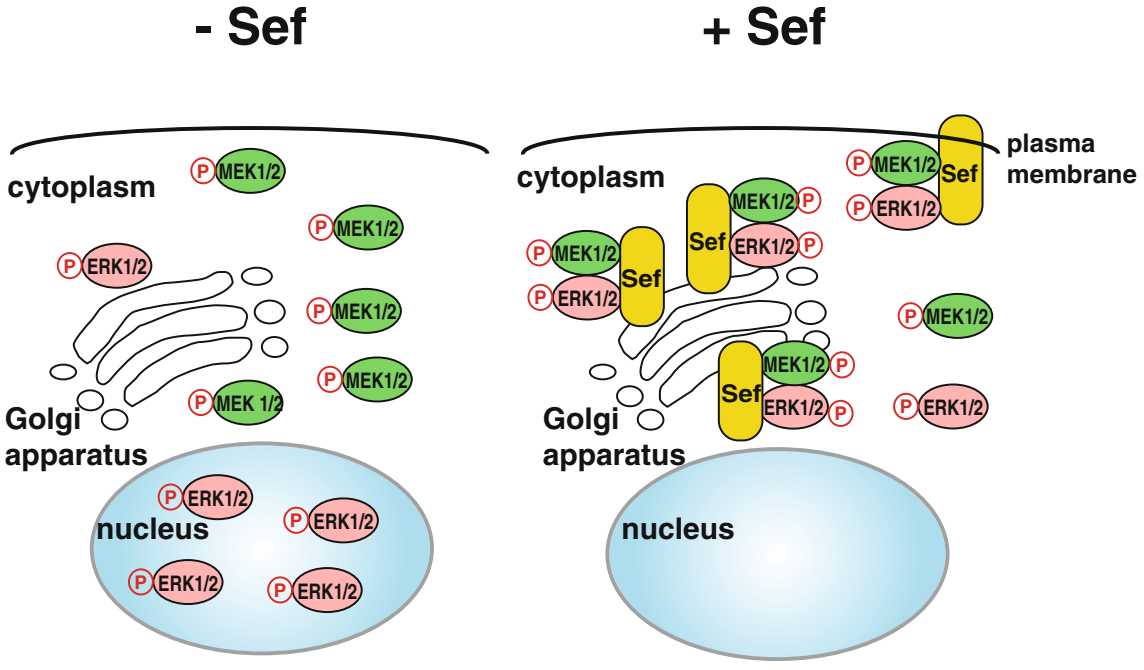

Fig. 2 Control of subcellular localization of ERK1/2 by Sef. In the absence of Sef, the MEK1/2/ERK1/2 complex is dissociated after stimulation and the dissociated ERK1/2 enters the nucleus as shown in Fig. 1. In the presence of Sef, Sef binds to activated MEK1/2 and ERK1/2 on the Golgi apparatus or the plasma membrane. Sef does not inhibit phosphorylation of ERK1/2 by MEK1/2 but inhibits the phosphorylation-dependent dissociation of the MEK1/2/ERK1/2 complex. Therefore, activated ERK1/2 remains in the cytoplasm. For details, see the text

the action of ERK1/2 on cytoplasmic substrates. Sef inhibits stimulus-dependent phosphorylation of Elk-1, but does not inhibit the stimulus-dependent phosphorylation of RSK2, a well-known cytoplasmic ERK1/2 substrate. Downregulation of endogenous Sef by siRNA enhances stimulus-induced ERK1/2 nuclear translocation and the activity of Elk-1 without affecting phosphorylation of both ERK1/2 and RSK2. Furthermore, Sef siRNA treatment enhances the expression level of ERK1/2 target genes, such as c-*fos*, *egr-1* and *junB*. These observations demonstrate that Sef is a specific inhibitor of Ras/MAPK signaling to the nucleus by targeting ERK1/2 to the cytoplasm. Recent reports demonstrate that part of Ras is located and activated on the Golgi apparatus in EGF-stimulated cells (Choy et al. 1999; Chiu et al. 2002; Bivona and Philips 2003; Bivona et al. 2003; Zhang et al. 2004). Sef on the Golgi apparatus could trap activated MEK1/2 and ERK1/2 downstream of Ras on the Golgi apparatus (Phillips 2004).

There is another known regulator of subcellular localization of ERK1/2. PEA-15, a small non-catalytic protein containing a death effector domain (DED), has been demonstrated to promote cytoplasmic localization of ERK1/2 (Formstecher et al. 2001). PEA-15 is expressed in a broad range of tissues, highly in brain astrocytes, and is shown to regulate TNF-induced apoptotic signaling and integrin activation (Danziger et al. 1995; Ramos et al. 1998; Kitsberg et al. 1999). PEA-15 contains an NES, binds to ERK1/2 and anchors ERK1/2 in the cytoplasm (Formstecher et al. 2001). Moreover, PEA-15 is shown to interfere with the ability of ERK2 to bind to nucleoporins (Whitehurst et al. 2004).

Spatial regulation of ERK1/2 in vivo

What is the physiological relevance of spatial regulation of ERK1/2? Prevention of nuclear translocation of ERK1/2 inhibits growth factor-induced gene expression and cell cycle entry (Brunet et al. 1999). Deletion of PEA-15 in astrocytes increases their proliferation, suggesting that cytoplasmic retention of ERK1/2 is important for astrocyte differentiation (Formstecher et al. 2001). More recent studies have revealed that subcellular localization of activated ERK1/2 is regulated in vivo. In the morphogenetic furrow of the developing Drosophila eye, activated ERK 1/2 is held in the cytoplasm for hours and then translocates to the nucleus (Kumar et al. 2003). If this "cytoplasmic hold" of activated ERK1/2 is disrupted, developmental patterning of the furrow is broken, suggesting that cytoplasmic retention of ERK1/2 has an essential function in vivo. In addition, a similar cytoplasmic hold of activated ERK1/2 is observed during mouse embryogenesis (Corson et al. 2003). Smith et al. (2004) performed detailed molecular observations about the spatial regulation of ERK1/2 in vivo by dealing with embryonic carcinoma (EC) cells. They have shown that endodermal differentiation of EC cells results in uncoupling ERK1/2 activation from phosphorylation and activation of Elk-1, although it does not cause the reduction of ERK1/2 activity. Interestingly, phosphorylation of RSK does not change during differentiation. Using cell fractionation and immunofluorescence microscopy, they have shown that nuclear translocation of activated ERK1/2 is impaired in EC cells. These studies, taken together, imply that spatial regulation of activated ERK1/2 plays an essential role in developmental processes.

Subcellular localization of other MAPKs

Regulatory mechanisms of subcellular localization and nucleocytoplasmic trafficking of JNK/SAPK and p38 have remained unclear. JNK/SAPK and p38 localize in both the cytoplasm and the nucleus (Cavigelli et al. 1995; Cheng and Feldman 1998). MKK4/7 and MKK3/6, the upstream activators of JNK/SAPK and p38, respectively, also localize in both the cytoplasm and the nucleus (Ben-Levy et al. 1998). Neither JNK/SAPK nor p38 has an obvious signal sequence for nuclear import or nuclear export. However, JNK/SAPK translocates to the nucleus by UV irradiation and osmotic stress (Cavigelli et al. 1995). Interestingly, the p38 target MAPKAPK-2, which has the NES sequence, binds to p38 and transports p38 to the cytoplasm (Ben-Levy et al. 1998; Engel et al. 1998). On the other hand, p38 translocates from the cytoplasm to the nucleus by hyperosmotic stress (Cheng and Feldman 1998). In budding yeast, subcellular localization of yeast p38 Hog1 is regulated by an active mechanism, though Hog1 does not have any nuclear localization signal (NLS) or NES sequence (Ferrigno et al. 1998). These studies raise the possibility that there are unknown mechanisms regulating the subcellular distribution of JNK/SAPK and p38.

Unlike other MAPKs, ERK5, the newest MAP kinase family member, has an NLS sequence in its C-terminal region. ERK5 localizes to the cytoplasm in quiescent cells and translocates to the nucleus upon stimulation (Yan et al. 2001; Esparis-Ogando et al. 2002). The mechanism for cytoplasmic localization of ERK5 in spite of the NLS has remained unclear.

Conclusion and perspectives

The MAPK signaling pathways regulate a vast array of cellular responses to extracellular stimuli. Spatiotemporal regulation of MAPK is important to transduce a lot of extracellular signals to correct regions in the cells with suitable timing. Recent studies have revealed several mechanisms of spatial regulation of ERK1/2. Sef and PEA-15 determine the destination of the signals, the nucleus or the cytoplasm, by regulating the localization of activated ERK1/2. Several reports provide evidence that subcellular localization of phosphorylated ERK1/2 is strictly regulated during developmental processes. The next challenges may include elucidation of regulatory mechanisms of Sef and PEA-15. Furthermore, it seems to be interesting to examine whether these spatial regulators of ERK1/2 are involved in the spatial regulation of ERK1/2 in developmental processes.

The regulatory mechanisms and significance of subcellular localization of the other MAPK family members have been unclear. ERK5 exhibits nuclear translocation from the cytoplasm upon stimulation, whereas JNK and p38 localize in both the cytoplasm and the nucleus. Uncovering the mechanism of ERK5 nuclear translocation might provide new insights into the significance of spatial regulation of MAPKs.

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