Combined Signaling through ERK, PI3K/AKT, and RAC1/p38 Is Required for Met-triggered Cortical Neuron Migration*5

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Cell migration is a complex biological process playing a key role in physiological and pathological conditions. During central nervous system development, positioning and function of cortical neurons is tightly regulated by cell migration. Recently, signaling events involving the urokinase-type plasminogen activator receptor, which is a key regulator for the activation of hepatocyte growth factor (HGF), have been implicated in modulating cortical neuron migration. However, the intracellular pathways controlling neuronal migration triggered by the HGF receptor Met have not been elucidated. By combining pharmacological and genetic approaches, we show here that the Ras/ERK pathway and phosphatidylinositol 3-kinase (PI3K) and mammalian target of rapamycin (mTOR) pathways are both required for cortical neuron migration. By dissecting the downstream signals necessary for this event, we found that Rac1/p38 and Akt are required, whereas the c-Jun N-terminal kinase (JNK) and mTOR/p70S6K pathways are dispensable. This study demonstrates that concomitant activation of the Ras/ERK, PI3K/Akt, and Rac1/p38 pathways is required to achieve full capacity of cortical neurons to migrate upon HGF stimulation.

Cell motility plays a key role during embryonic development, adult physiology, and pathological events. During central nervous system development, neuronal migration is essential to ensure proper positioning of neurons in the mature brain (1). In agreement with this, defects in cell migration can result in brain abnormalities and pathologies (2–4). While a wide range of growth factors are well known to control motility of different cell types, those involved in neuronal migration have not yet been fully characterized. Genetic studies have contributed to identify growth factor signals as modulators of cell migration in developing brains. For example, fibroblast growth factor-2 as well as members of the neurotrophin family, brain-derived neurotrophic factor and neurotrophin-4, are mediators of cortical neuron migration in vivo (5–7).

Recent studies have also suggested that hepatocyte growth factor (HGF)5 signaling can elicit trans-encephalic migration of interneurons during forebrain development. In particular, mice lacking the urokinase-type plasminogen activator receptor (u-PAR), which is a key component of HGF activation, exhibit deficient scatter activity of neurons in the forebrain and reduced number of interneurons in the frontal and parietal cortex, possibly due to aberrant interneuron migration from the ganglionic eminence (8, 9). Consistently, the HGF receptor tyrosine kinase Met is expressed in cortical neurons and the ability of HGF to induce their migration has been investigated in vitro using the Boyden chamber assay (10). In addition to the motogenic activity, several reports have enlightened the pleiotropic functions triggered by the HGF/Met couple in several types of neurons. For example, HGF is an axonal chemoattractant and neurotrophic factor for motor neurons (11–13) and is required in vivo for recruitment of motor neurons during motor pool specification (14). Moreover, HGF controls survival and axonal growth of dorsal root ganglia sensory neurons (15) and elicits multiple functions in sympathetic neurons (16–18). The large range of HGF activities and its observed synergy with other neurotrophic factors shows that HGF signaling acts predominantly to potentiate the response of different neurons to specific signals (19). However, which signaling pathways are required for these biological responses triggered by Met in neurons still remains elusive.

Upon HGF stimulation, Met activates multiple downstream signals through its multifunctional docking site located at its carboxyl-terminal tail (20–22). A wide range of signaling players involved in cell motility induced by HGF have been identified using several cell lines (22–28).

For example, activation of PI3K signaling by Met triggers motogenic responses in fibroblasts and epithelial and muscle cells (29–32). Among the PI3K effectors, Akt and Rac1 have been proposed to modulate HGF-dependent cell motility (23, 25, 29, 33, 34). The contribution of the Ras/ERK pathway for cell migration triggered by Met appears to be dependent on the cellular context, since ERK activation is required for migration of MDCK cells (25), while it is dispensable for striatal progenitor cells (35).

Loss-of-function studies have demonstrated the motogenic activity of the HGF/Met system in vivo. In particular, during mouse embryogenesis Met signaling is required for myoblast migration (11, 36, 37). Genetic analysis of met specificity-switch mutant mice has been instrumental for studying signaling requirement for myoblast migration in vivo. In these mice, the multifunctional docking sites of Met have been replaced by specific binding motifs for PI3K (Met2P) or Src (Met2S) (38). Myoblast migration is strongly reduced in both met2P/2P and met22/22 mutants, thus showing that myoblast migration requires a more complex signaling network triggered by Met (38). However, the early embryonic lethality of met mutants has prevented to further study the motogenic activity of other cell types like neurons in vivo.

M6K, mitogen-activated protein kinase/extracellular signal-regulated kinase kinase; GFP, green fluorescent protein; dn, dominant negative; ca, constitutively active; PBS, phosphate-buffered saline.

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5 The abbreviations used are: HGF, hepatocyte growth factor; PI3K, phosphatidylinositol 3-kinase; DMEM, Dulbecco’s modified Eagle’s medium; ERK, extracellular signal-regulated kinase; JNK, c-Jun N-terminal kinase; mTOR, mammalian target of rapamycin;
We are studying signaling mechanisms involved in cortical neuron migration induced by Met. To identify the signaling requirement, we compared the HGF-induced migration of wild-type cells to that of met specificity-switch mutant cells. In addition, the use of pharmacological inhibitors allowed us to specifically interfere with downstream signals activated by Met. Here we demonstrate that Ras/ERK and PI3K pathways are both required for the motogenic activity of cortical neurons triggered by Met, as inhibition of either one of these pathways prevents their migration. Moreover, expression of a constitutively active form of PI3K in cortical neurons with deficient Met-triggered PI3K signaling and cell motility completely rescues migration defects. We further investigated the downstream signals necessary for this event and found that while both Rac1/p38 and Akt are required for cortical neuron migration, c-Jun N-terminal kinase (JNK)/Jun and mTOR/p70s6k pathways are not. Together, these data demonstrate that concomitant activation of the Ras/ERK, PI3K/Akt, and Rac1/p38 signals is required to achieve full capacity of cortical neurons to migrate in response to HGF.

MATERIALS AND METHODS

Reagents and Antibodies—Human recombinant HGF (R&D Systems) was used at a concentration of 50 ng/ml unless specified. The pharmacological inhibitors LY294002 (PI3K inhibitor), rapamycin (mTOR inhibitor) and U0126 (MEK inhibitor) were purchased from Calbiochem. SB203580 (p38 inhibitor) and J-NIK-1 (JNK inhibitor) were purchased from Alexis Biochemicals. The concentrations of each inhibitor are indicated in the figures. No toxic effects were observed at the concentrations used. The antibodies used were anti-pAkt (Ser473), anti-p-p70S6K (Thr422/Tyr424), anti-p-p38 (Thr180/Tyr182), and anti-p-ERK (Thr202/Tyr204, clone E10) (Cell Signaling), anti-phosphotyrosine (clone 4G10, anti-pY), anti-pJun (Ser73) (Upstate Biotechnology), anti-mouse-Id (clone 129/sv background were intercrossed with heterozygous males on mixed C57Bl/6 background and all experiments were performed in accordance with institutional guidelines.

Cortical Neuron Culture—Neocortices were dissected from 15-day-old wild-type or met2P/2P knock-in signaling mutants were previously described (38). To partially rescue placental development, heterozygous males on a mixed C57Bl/6 background were intercrossed with heterozygous females on outbred strain CD1 (38). Mice were kept at the Institute for Developmental Biology of Marseille animal facilities, and all experiments were performed in accordance with institutional guidelines.

Cortical Neuron Culture—Neocortices were dissected from 15-day-old wild-type or met specificity-switch mutant embryos and digested with trypsin-EDTA for 15 min at 37 °C. Cortical neurons were washed twice with DMEM/F-12 medium supplemented with 10% horse serum (DMEM/HS). For biochemical studies, dissociated cells were seeded on poly-d-ornithine (poly-O, Sigma)-coated 6-cm diameter dishes at a density of 6 × 10⁴/dish in DMEM/HS. Four hours later, the medium was replaced by neurobasal medium supplemented with B27 nutrient (NB/B27; 50/1; Invitrogen). Cells were cultured for 3 days (3DIV) unless specified. Treatment with specific inhibitors was performed 2 h before HGF stimulation. For electroporation experiments, cortical neurons (2 × 10⁴) were electroporated in the presence of 4 μg of expression plasmid using the Electro square porator™ BTX-ECM830 (Genetronics Inc.). Electroporation conditions were 5 pulses at 270 V of 3 ms separated by a 1-s interval. Cells were then placed for 10 min on ice and submitted to migration assay.

Migration Assay—Cell migration was assayed using 24-well poly-O-coated-Bedoyen chambers (5 μm pore, Costar), which allows testing chemotactic response of HGF rather than a simple motile response. Cells (2 × 10⁵) were seeded in NB/B27 medium on the upper side of the chamber. The lower compartment contained NB/B27 medium supplemented or not with HGF (50 ng/ml) and chemical inhibitors, as specified. The assays were performed for either 24 or 48 h with non-electroporated or electroporated cells, respectively. Cells were then fixed with 4% paraformaldehyde (Sigma) for 30 min at 4 °C. Boyden chamber filters were mounted on glass coverslips in presence of vectashield® Dapi (Vector). The number of migrating cells (on the lower side of the filter) was directly analyzed under a Zeiss Axioshot fluorescent microscope and determined in at least five fields of each filter. All cell migration assays were performed in triplicate. Statistical comparisons were made using the paired Student’s t test.

PI3K Assay and Western Immunoblotting—PI3K assays were performed as described previously (38). Briefly, cortical neuron lysates were subjected to immunoprecipitation with anti-pY antibodies, and PI3K activity was assayed using phosphatidyserine, phosphatidylinositol, and [γ-32P]ATP. Phosphorylated lipids were then extracted and separated by liquid chromatography on a silica plate. Signals were detected by autoradiography.

Procedures of cell lysis, immunoprecipitation, and Western blotting have been described previously (38). Briefly, cortical neuron cultures were lysed in either ice-cold EBH lysis buffer (20 mM Tris-HCl, pH 7.5, 150 mM NaCl, 5 mM EGTA, 5 mM EDTA, 10% glycerol, 1% Triton X-100) supplemented with protease inhibitors (5 μg/ml leupeptin, 5 μg/ml pepstatin, 2 μg/ml aprotinin, 5 mM benzamidin, 1 mM phenylmethylsulfonyl fluoride) and phosphatase inhibitors (10 mM sodium fluoride, 1 mM sodium pyrophosphate, 1 mM orthovanadate, 10 mM glycerophosphate) or boiling total protein extraction buffer (TPEB: 5% SDS, 250 mM Tris-HCl, pH 6.8). For immunoprecipitation, cell lysates (300 μg) were incubated 2 h at 4 °C with anti-Met antibodies coupled to protein A-Sepharose in EBH lysis buffer. Immunocomplexes or total cell lysates (30–50 μg) were separated on SDS-PAGE, proteins were electrotransferred onto a polyvinylidene difluoride membrane (Immobilon-P, Millipore), and membranes were saturated in PBST (PBS, 0.1% Tween) supplemented with either 5% milk or 3% bovine serum albumin. After overnight incubation with primary antibodies, membranes were washed with PBST and incubated with secondary antibodies. Signals were detected with enhanced chemiluminescence system (Amersham Biosciences).

Rac1 Activity Assay—Rac assay was performed as described previously (42). Briefly, after HGF stimulation, cells were chilled on ice, then lysed in buffer containing 50 mM Tris-HCl, pH 7.0, 500 mM NaCl, 0.5% Nonidet P-40, 10% glycerol, 1 mM EGTA, 1 mM MgCl₂, supplemented with protease inhibitors. Cell lysates (600 μg) were incubated 45 min at 4 °C with recombinant GST-PBD coupled to glutathione-Sepharose beads. Immunocomplexes were separated on SDS-PAGE and analyzed by Western blotting using a monoclonal anti-Rac antibody.

RESULTS

ERK Signaling Is Required for Cortical Neuron Migration Induced by HGF—Although several reports have shown that the Ras/ERK pathway contributes to Met-triggered cell migration in epithelial cells (25, 27, 29, 43), this signal is dispensable for HGF-induced migration of striatal
that in contrast to primary embryonic hepatocytes (38), both Met2P and Met2S efficiently induced ERK phosphorylation similar to wild-type Met (Fig. 1B). Unexpectedly, we found that in contrast to primary embryonic hepatocytes (38), both Met2P and Met2S allowed us to investigate its requirement for cortical neuron migration, using Boyden chamber assay. As shown previously (10), HGF treatment induced wild-type cortical neuron migration. Fig. 2A shows that HGF stimulation induced sustained PI3K activation in wild-type and met2P/2P cortical neurons but not in met2S/2S mutant cells.

The inability of met2S/2S neurons, with deficient PI3K activity, to migrate in response to HGF suggests that PI3K can be a crucial signaling molecule for HGF-dependent motility. We therefore assayed cell migration in the presence of the PI3K inhibitor LY294002 (supplemental Fig. 2B). Both wild-type and met2P/2P mutant cells failed to migrate in the presence of LY294002 (Fig. 2B), demonstrating the essential role of the PI3K pathway for this event.

We asked whether adding back a constitutively active form of PI3K in met2S/2S mutant neurons was sufficient to restore motility induced by HGF. Cell migration was assayed in neurons electroporated with a constitutively active form of PI3K (caPI3K) (44). In the absence of HGF, expression of caPI3K partially increased the basal level of migration in wild-type and met2P/2P cortical neurons but not in met2S/2S mutant cells.

Intact PI3K Signaling Is Necessary for Met-triggered Cortical Neuron Migration—The above results argue that in addition to Ras/ERK, at least another pathway is required for Met-triggered cortical neuron migration. Fig. 1C shows that met2P/2P cortical neurons migrate in response to HGF. The retained ability of Met to signal through PI3K in these cells (38) allowed us to test whether this pathway is an essential modulator of neuronal migration. We first assessed the ability of met2S/2S mutant neurons to migrate in response to HGF, showing that the Met2S context, the level of PI3K activation could be
determinant for the migration capacity. Remarkably, caPI3K fully restored migration of met2S/2S mutant neurons treated with HGF (p < 0.001) (Fig. 2C). These results show that the missing signal in met2S/2S cortical neurons is the PI3K pathway. Interestingly, neuronal migration of met2S/2S mutant cells electroporated with caPI3K was abolished in the presence of the MEK inhibitor U0126 (p < 0.001) (Fig. 2D). Together, these results genetically demonstrate that intact PI3K signaling is essential for cortical neuron migration triggered by Met. Moreover, they also show that concomitant activation of both Ras/ERK and PI3K pathways is required.

**Activated Akt, but Not mTOR/p70s6k Pathway, Contributes to HGF-mediated Cortical Neuron Migration**—We next aimed at identifying which effectors of PI3K are required for Met-triggered neuronal migration. It has been recently reported that the PI3K downstream effector Akt (44), in addition to control cell survival (45–47), can also modulate cell migration (48–50). HGF treatment induced transient Akt phosphorylation in wild-type neurons (supplemental Fig. 2C). Akt phosphorylation was severely reduced in met2S/2S mutant neurons compared with wild-type cells (Fig. 3A), as previously found in hepatocyte cultures (38).

The requirement of Akt for HGF-triggered cortical neuron migration was analyzed by electroporating a dominant negative form of Akt (dnAkt) in wild-type and met2S/2S mutant neurons. dnAkt reduced HGF-induced neuronal migration of wild-type cells, with intact Akt signaling (Fig. 3B). In contrast, it did not alter migration of met2S/2S mutant neurons, with defective Akt signaling (Fig. 3B). These results genetically show that although Akt contributes to cortical neuron migration triggered by Met, its full activation is not required.

**Inhibition of Rac1/p38 Signaling Impairs Cortical Neuron Migration Triggered by Met**—We next assayed whether two other MAPKs, p38 and JNK, which are known to modulate motility of various cell types (52–55), are activated and required for Met-triggered cortical neuron migration. HGF treatment induced JNK activity (supplemental Fig. 3A) and transient Jun phosphorylation in cortical neurons (Fig. 4A). However, treatment of cultures with JNK inhibitors (D-JNKI-1 and L-JNKI-1) abolished JNK activity (supplemental Fig. 3A) but did not interfere with HGF-induced neuronal migration (for D-JNKI-1 see Fig. 4B; for L-JNKI-1: data not shown) (p = 0.357), demonstrating that although the
JNK/Jun pathway is activated by HGF in cortical neurons, it is not required for their migration.

HGF stimulation also induced activation (supplemental Fig. 3B) and phosphorylation of p38 with similar kinetics in wild-type and met2P/2P mutant neurons but not in met2S/2S mutant cells (Fig. 4C). Interestingly, blocking p38 activity using SB203580 (supplemental Fig. 3, B and C) completely inhibited cortical neuron migration induced by HGF (Fig. 4D). To further emphasize the relevance of p38 signaling, we tested whether Rac1, a well known p38 upstream regulator, was activated by HGF in cortical neurons. HGF treatment induced transient Rac1 activation (Fig. 4E). We then assessed the ability of a mutant form of Rac1 to block cortical neuron migration. Wild-type and met2P/2P cortical neurons electroporated with a dominant negative form of Rac1 (dnRac) failed to migrate upon HGF stimulation (Fig. 4F). Thus, intact Rac1/p38 signaling pathway is required for cortical neuron migration induced by HGF. Electroporation of a constitutively active form of Rac1 (caRac) in wild-type neurons did not significantly change their migratory capacity upon HGF stimulation (Fig. 4F; p = 0.5). Interestingly, the partially reduced motility of HGF-treated met2P/2P neurons was restored by caRac (Fig. 4F; p = 0.291), suggesting that in the Met2P context, activation of molecules other than Rac1 are required to reach full migratory capacity. Moreover, overexpression of a constitutively active form of Rac1 in met2S/2S mutant neurons partially restored their motility induced by HGF (Fig. 4F; p < 0.001), further emphasizing the requirement of Rac1 activity for proper cortical neuron migration triggered by Met. Together, these results show that while caPI3K is sufficient to fully restore migration of met2S/2S cortical neurons, Rac1 is required together with other signals, distinct from RhoA (supplemental Fig. 3D), possibly Akt. In conclusion, our data show that the HGF/Met motogenic activity in cortical neurons requires activation of a specific set of signaling networks composed of the Ras/ERK, PI3K/Akt, and Rac1/p38 signals.

**DISCUSSION**

The motogenic activity induced by HGF/Met has been studied in various physiological contexts, such as scattering of epithelial cells, embryonic myoblast migration, and migration of neocortical neurons during brain development (8, 11, 22, 36, 60). The understanding of signaling mechanisms activated by Met during cell migration in the nervous system is much less advanced compared with cells of other origin. Moreover, the signaling mechanisms activated by Met to trigger migration might be redefined according to the cell types. Using genetic and pharmacological approaches, we show here that both Ras/ERK and PI3K pathways are simultaneously required for cell migration, since inhibition of one signaling route is sufficient to perturb motility of neurons (Fig. 5). While these two pathways can modulate each other in other cells (61, 62), we found that in cortical neurons they are parallel pathways (Fig. 5), since inhibition of one does not alter activation of the other (supplemental Fig. 2, A and B). We also found that Akt, but not mTOR/p70S6K, contributes to neuronal migration induced by HGF (Fig. 5). Moreover, intact Rac1/p38 pathway is also essential (Fig. 5). Thus, full migratory capacity of cortical neurons triggered by Met is achieved by concerted activation of distinct signals.

The requirement of PI3K for HGF-mediated cortical neuron migration is in agreement with recent studies by Konno et al. (63) showing that in utero electroporation of a dominant negative form of PI3K blocks radial migration of cortical neurons. One PI3K effector found involved in radial migration was Rac1. In our system, we also found that Rac1 is essential for Met-triggered cortical neuron migration. It is possible that in this cellular context, Rac1 is one PI3K effector required for neuronal migration induced by HGF.

The Rac1 downstream effector p38 is also essential for HGF-mediated motogenic activity. Recent studies have shown that p38 activation contributes to HGF-induced migration of corneal epithelial cells (64).
How p38 controls cell migration is still not clear. One possibility is that p38 modulates cytoskeleton rearrangements through phosphorylation of heat shock protein 25 (65–68). The involvement of JNK signaling during cell migration has been enlightened by showing that in utero electroporation of a dominant negative form of JNK delays radial migration in the cerebral cortex (69). Our findings demonstrate that neuronal migration triggered by Met discriminates between signals known to be involved in cell migration in the cortex: JNK is not involved, whereas p38 is required.

We also found that the downstream PI3K effector Akt contributes to cell migration. Although the link between Akt activation and induction of cell motility has been suggested (33), there was no proof for its direct involvement in HGF-mediated cell migration. Here we demonstrate that altered Akt signaling (in the Met<sup>2P</sup> context) correlates with reduced cell motility induced by HGF. Akt can control cell motility through the mTOR/p70<sup>S6K</sup> pathway (70, 71), which can modulate cytoskeleton rearrangement (52, 72). However, this mechanism seems not involved in our system since inhibition of the mTOR/p70<sup>S6K</sup> pathway by rapamycin did not perturb cortical neuron migration. Another mechanism by which Akt can modulate cell migration is through inhibition of its downstream target GSK-3β (73), which correlates with microtubules...
stabilization, thus favoring cell polarity and migration (74). Whether GSK-3β is involved in HGF-dependent cortical neuron migration remains to be determined.

Our studies also contribute to further understand how Met signaling changes according to the cellular context. Interestingly, we found several differences with respect to other primary embryonic cells (38): 1) differences in the kinetics of activation (transient ERK phosphorylation in cortical neurons, sustained in hepatocytes); 2) ability of different Met mutants to activate a given pathway (levels of ERK phosphorylation triggered by met mutant cortical neurons were similar to wild-type cells, while reduced in embryonic hepatocytes); 3) difference in the signaling requirement for cell migration (motility is induced in met2P/2P but not in met25P/25 cortical neurons, while it is severely affected in both met mutant myoblasts). Thus, our data strongly support the concept that the read out of receptor tyrosine kinase activation is differently interpreted accordingly to the cell type and that requirement of downstream signals for a given biological response is redefined by the cellular context.

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