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Citation
Krens, S. F. G., Spaink, H. P., & Snaar-Jagalska, B. E. (2006). Functions of the MAPK family in vertebrate development. *Febs Letters*, *580*(21), 4984-4990. doi:10.1016/j.febslet.2006.08.025

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FEBS Letters 580 (2006) 4984–4990

Minireview

Functions of the MAPK family in vertebrate-development

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Received 23 May 2006; revised 7 July 2006; accepted 15 August 2006

Available online 28 August 2006

Edited by Angel Nebreda

Abstract The mitogen activated protein kinase (MAPK) family, consisting of the extracellular signal regulated protein kinase, c-Jun amino terminal MAPK and p38 subfamilies, is conserved in evolution throughout the plant and animal kingdoms. These proteins have been implicated in diverse cellular processes including cell growth, migration, proliferation, differentiation, survival and development. Gene-targeting approaches in mice, chickens, frogs and zebrafish revealed crucial roles of MAPK in vertebrate development. Gene-disruption or -silencing often lead to lethal effects, therefore the zebrafish ex utero development provides an excellent in vivo model to study the function of MAPK in early embryogenesis. In this review, we summarize the current understanding of the MAPK family function in vertebrate-development and place this into the perspective of possibilities for future research.
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Keywords: Mitogen activated protein kinase; Extracellular signal regulated protein kinase; c-Jun amino terminal MAPK; p38; Development; Vertebrates; Zebrafish

1. Introduction: The MAPK pathway

The mitogen activated protein kinase (MAPK) family is conserved in evolution and is involved in diverse cellular processes including cell growth, proliferation, differentiation, survival, innate immunity and development [1–3].

MAPKs transmit signals in the form of sequential phosphorylation events. The phospho-relay system is composed of three kinases: a MAPK kinase kinase (MAPKKK), a MAPK kinase (MAPKK) and a MAPK. Phosphorylation of the MAPKs occurs on a conserved dual-phosphorylation domain (Thr-Xxx-Tyr) leads to activation of the protein (Fig. 1) and the subsequent formation of dimers which translocate into the nucleus to activate downstream targets [1–3]. Three major subfamilies of MAPK proteins have been defined: extracellular signal regulated kinases (ERK), the c-Jun amino-terminal kinases (JNK), and the p38 MAP kinases. The middle amino-acid residue of the conserved Thr-Xxx-Tyr dual-phosphorylation domain designates a MAPK protein to one of these subfamilies. In general, the ERK subfamily (TEY) is mainly activated by growth factors, p38 (TGY) by stress factors and JNK (TPY) are activated by stress-, differentiation- and growth-factors [4–6]. It should be stressed here that scaffold proteins play an important role in the spatial–temporal organization of signaling complexes leading to activation of a specific cascade [1,6,7].

To illustrate the evolutionary conservation of the MAPK family, we constructed a phylogenetic tree of the vertebrate MAPKs by the neighbor-joining method (Fig. 2) [8]. This analysis was performed by multiple alignments with the amino acid sequences of the different vertebrate MAPKs from human, rat, mouse, *Xenopus* and zebrafish. As expected from the evolutional point of view the different vertebrate MAPKs cluster with their corresponding orthologs, which are also indicated by their MAPK-family number (MAPK1–15).

Currently, based on phosphorylation consensus, sequence identity, signaling profile and functions, six different MAPK cascades have been identified in mammals: ERK1/2, ERK3/4, ERK5, ERK7/8, JNK1/2/3, and p38-isoforms α/β/γ(ERK6)/δ [1–3] (Fig. 3). The best studied ERK1 and ERK2 are activated by the upstream MAPKKs MEK1 and MEK2, while MEK1-2 are in turn activated by their upstream MAPKKKs or Raf protein kinases. Interestingly, ERK3 is a ubiquitously active MAPK and its activity is regulated by protein stability. The mechanisms of regulation for ERK4 are still largely unclear. In addition, ERK5 is exclusively activated by MEK5, which can be phosphorylated by the MAPKKKs MEKK2 and MEKK3. ERK7 is similar to ERK3 in that it is constitutively activated, presumably by the C-terminus of the protein. ERK7 activity is not regulated by extracellular stimuli. Despite intensive efforts, the activators for ERK8 are yet unknown, although ERK8 is shown to be activated after long stimulations with serum and in cells expressing the oncogene v-src, suggesting that ERK8 is involved in long term

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Abbreviations: ASK1, apoptosis signal-regulating kinase 1; A-Raf1, V-RAF murine sarcoma 3611 viral oncogene homolog 1; B-Raf, V-RAF murine sarcoma viral oncogene homolog B1; BMK1, big MAP kinase 1; CLIC3, chloride intracellular channel 3; Cot, Cancer Osaka Thyroid Oncogene (=Tpl-2); ERK, extracellular signal regulated protein kinase; JNK, c-Jun amino terminal MAPK; MEK, MAPK/ERK kinase; MEKK, MEK kinase; MAPK, mitogen activated protein kinase; MK, MAPK-activated protein kinases; MKK, MAPK kinase; MKKK, MAPK kinase kinase; MLK2,3, mixed-lineage protein kinase 3; Mos, V-MOS moloney murine sarcoma viral oncogene homolog; Myf5, myogenic activator 5; POSH, plenty of SH3s; Raf1, V-RAF murine leukemia viral oncogene homolog 1; SAPK, stress activated protein kinase; Tpl-2, tumor progression locus 2; TAO1,2,3, thousand and one amino acids; TAK1, TGFβ activated kinase; v-src, avian Sarcoma (Schmidt–Ruppin A-2) viral oncogene

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doi:10.1016/j.febslet.2006.08.025

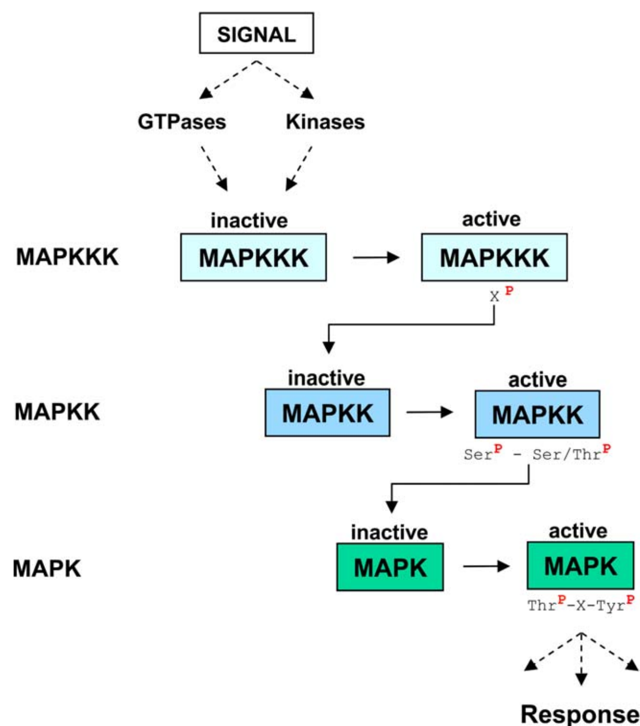

Fig. 1. The mitogen activated protein kinase module. The MAPK module consists of three kinases: a MAPKKK, a MAPKK and a MAPK. Different MAPK cascades can be activated by various signals. Upon activation the upstream kinase activates the downstream kinase by phosphorylation and leads to a response.

signaling. Similar to ERKs, the p38-MAPK module includes a range of MAPKKKs such as MEKK1-4, MLK2-3, apoptosis signal-regulating kinase 1 (ASK1) and TGFβ activated kinase (TAK1). These activate the MAPKKs MEK3 and MEK6, resulting in the activation of the p38 α, β, γ, δ isoforms. The JNK MAPKs are activated by the MAPKKs MEK4 and 7, which are in turn activated by the MAPKKKs MEKK1-4, MLK2-3, TAO1-2, TAK1 and ASK1-2 [2,6,9,10]. Details of the molecular mechanisms governing the developmental functions of different MAPK-cascades in vertebrate models are beginning to emerge and will be discussed in the following sections (Figs. 2 and 3).

2. ERK1/2

ERK1 (MAPK3, p44MAPK) was the first identified MAPK [11]. Until now, homologs for *erk1* have been reported for human, mouse, rat and zebrafish genomes. ERK1 and ERK2 are the most intensively studied MAPKs in developmental processes. Detailed immuno-histochemical analysis revealed localized spatio-temporal patterns of ERK1/2 phosphorylation during mouse [12], chicken and zebrafish development, with FGF as most predominant activator during development. *Erk1−/−* mice are viable, fertile and of normal size [13]. The proliferation and maturation of the thymocytes is affected, despite expression of ERK2. Mice lacking ERK1 also manifest abnormal signaling responses, which are linked to an upregulation of ERK2 activity in the brain. ERK1 has a critical regulatory role in brain long-term adaptive changes underlying striatum-dependent behavioral plasticity and drug addiction [14]. Furthermore, ERK1 is an important modulator of synaptic plasticity. The existence of the distinct scaffold MP1 for ERK1-MEK1 indicates specific functions and location for MEK1/ERK1 complex [15]. The MP1 scaffold was initially identified by its capability to bind to the proline-rich region of MEK1 and to be involved in the activation of ERK1, but not ERK2 signaling [1,15].

ERK2 (MAPK1, p42MAPK) is found in human, mouse, rat, frog, chicken and zebrafish genomes. Importantly, mouse embryos lacking exon 2 of the *erk2* gene die in utero before embryonic day (E) 8.5 due to a defect in trophoblast development [16]. *Erk2*-deficient mice fail to form the ectoplacental cone and the extra-embryonic ectoderm, which gives rise to mature trophoblasts in the fetus. In addition *Erk2−/−* embryos also fail to form mesoderm, based on histological criteria at E6.5 and E7.5 [17,18]. Significantly, ERK1 is incapable of compensating for ERK2 function in *erk2−/−* mice, suggesting that the observed effect is ERK2 specific and cannot be rescued by ERK1.

Despite effort, in frog and chicken no *erk1* gene has been found until now. However, the ERK1 protein has been detected by Western-blot analysis in chicken, where p-ERK1/2 expression was observed in motor axons, but not in sensory axons. In a follow up study Kato and co-workers have also demonstrated specific activation of ERK1/2 in growing motor axons suggesting that p-ERK1/2 may be involved in outgrowth and/or guidance of this subset of axons [19]. In contrast, modulation of ERK2 activity affects mesoderm differentiation in *Xenopus* embryos, whereas inhibition of the ERK2 activation prevents animal caps to differentiate into mesoderm tissues [20]. Elevated ERK activation is also detected by immuno-histochemistry during segmentation in mouse, chicken and zebrafish [21].

In zebrafish, the presence of the ERK-MAPK cascade was first shown by Western-blot analysis, where insulin-like growth factors (IGFs) stimulates zebrafish cell proliferation by activating MAPK and PI3-kinase signaling pathways [22]. Subsequently it was shown that chitin oligosaccharides, activate ERK1 and ERK2 in zebrafish cells, via the Ras-Raf-MEK module [23]. The developmental roles of ERK1 and ERK2 in zebrafish development have mostly concentrated on the functions of the FGF/MAPK pathway, which also contains the inhibitors Sef [24,25], Sprouty2/4 and the MAPK phosphatases MKP1 and MKP3 [26]. Overactivation of the Fgf/ERK-pathway leads to dorsalized embryos by inhibiting expression of *bmp* genes [27]. Overexpression of ERK-MAPK phosphatase MKP3 or injection of a high dose of mRNA of the inhibitor Sef also results in an opposite ventralization [24,28]. This implies that manipulation of ERK-MAPK activation affects zebrafish development. It can therefore be suggested that ERK1/2 in zebrafish are regulated via canonical pathways, but precise regulation and distinguished developmental function for ERK1 and ERK2 remain to be defined. Recently, a developmental role for ERK1 in axial mesoderm formation was demonstrated and the absence of active ERK2 in the blastula-margin blocked the initiation of epiboly cell migration, disturbed the microtubule organization and led to an arrest of embryogenesis, preventing further differentiation of epiblast and hypoblast (unpublished data). Similarly to mice also in zebrafish ERK1 is not able to rescue developmental phenotypes caused by ERK2 knock-down.

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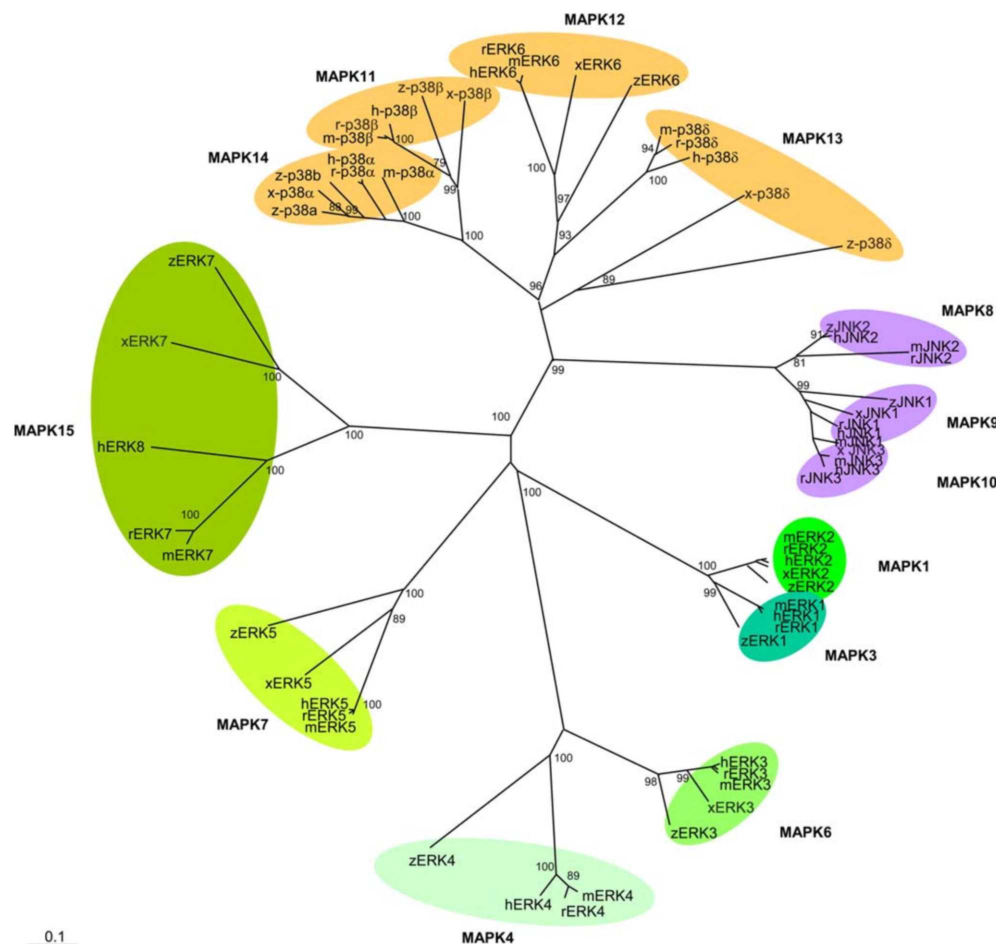

Fig. 2. Phylogenetic tree of the vertebrate MAPKs. The phylogenetic tree was constructed by the neighbor-joining method of the amino acid sequences of the different vertebrate MAPKs using Clustal W, available at the web server of the DNA Data Bank of Japan (DDBJ, http://hypernig.nig.ac.jp). Clustal W analysis was done using default settings, without Kimura's correction. Bootstrap sampling was reiterated 10000 times. For the matrix table 'blosum' was used. The gap extension penalty was set at 0.2 and the gap distance was set at 8. Trees were printed using the program Treeview (http://taxonomy.zoology.gla.ac.uk/rod/treeview.html). The phylogenetic tree illustrates the evolutionary conservation of the MAPK family members in human (h), rat (r), mouse (m), *Xenopus laevis* (x) and zebrafish (z). The different MAPKs cluster together and are indicated by their MAPK-family number (MAPK1–15). *Black* text = previously annotated and shown to be expressed; *gray* text = translation of genomic prediction. The predicted sequences were found in the following versions of the genomes of the Sanger Ensembl: *Rattus norvegicus* = v38, *Xenopus* = v38; zebrafish = Zv6.

3. ERK3/4

Interestingly, ERK3 and ERK4 are the only ERK-MAPKs that lack the characteristic TEY activation motif, but display a SEG activation domain (Fig. 3). Only the serine residue in this SEG-motif can be phosphorylated. ERK3 has a characteristic 400 amino acid C-terminus, which is partly homologous to ERK4 (170 amino acids). The stimulants for ERK3 and ERK4 have not been identified, so far.

ERK3 (MAPK6, p97MAPK) has been reported for human, mouse, rat, zebrafish and gene-predictions were also found in the frog and chicken genomes (Fig. 2). ERK3 seems to be mainly regulated by its protein stability and auto-phosphorylation. Human ERK3 interacts with MAPK-activated protein 5 (MK5 or PRAK) and spatio-temporal expression of ERK3 and MK5 suggest co-expression of both kinases [29]. In mice, deletion of *mk5* leads to strong reduction of ERK3 protein levels and is lethal around E11, the time-point where expression levels of *erk3* are maximal in wildtype mouse embryos [29,30]. This suggests an universal role of this MK5-ERK3 module in development. *Erk3−/−* mice have been made, although their phenotypes are not described in literature yet (Turgeon B and Meloche S, manuscript in preparation) [29].

ERK4 (MAPK4, ERK3-related, ERK3-beta, p93MAPK), closely related to ERK3 [31], was first identified in human [32], and subsequently described for mouse, rat, and zebrafish. A predicted ORF was also found in the chicken (Fig. 2). Its spatio-temporal expression-pattern is predominantly localized in the brain during zebrafish development [33]. However, a developmental function of this MAPK remains to be determined.

4. ERK5 (MAPK7, BMK1)

ERK5, also referred to as big MAP kinase 1 (BMK1), is found in human, mouse, rat, frog and zebrafish. Activation of ERK5 is mediated by MEK5. The ERK5 pathway is activated by oxidative stress, hyper-osmolarity and growth factors [34]. ERK5 has a unique carboxy-terminal domain, which

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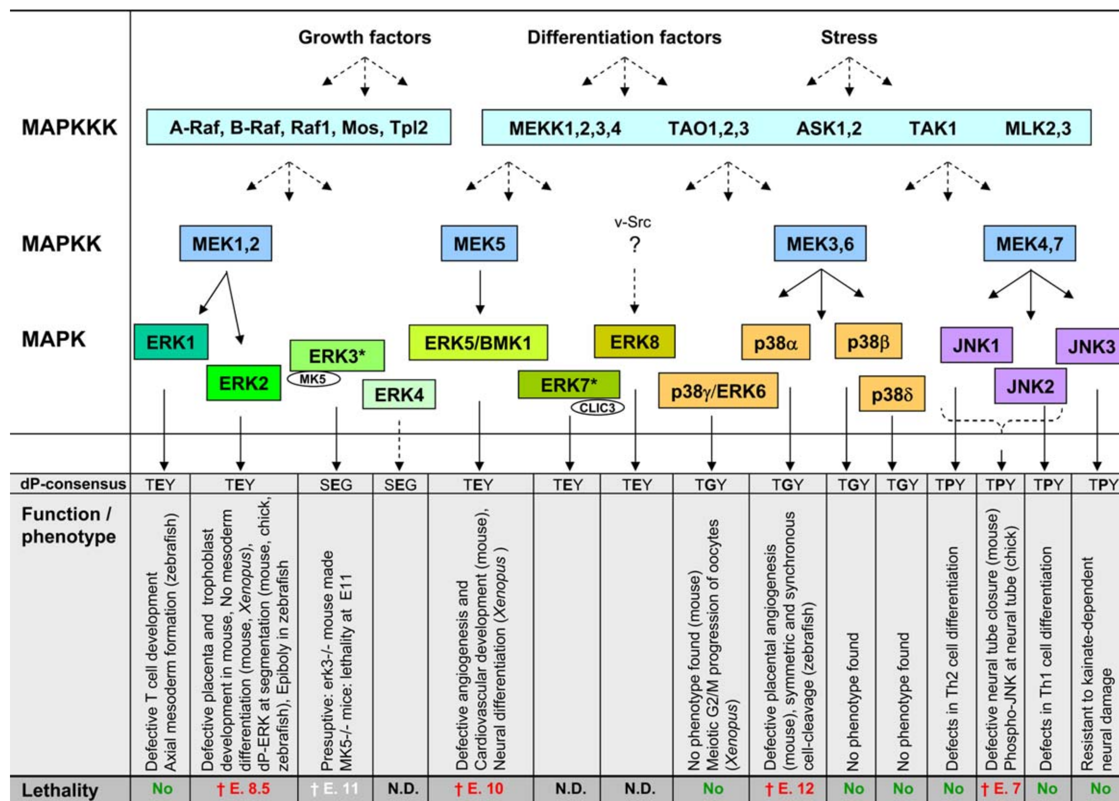

Fig. 3. The mitogen activated protein kinase module and the developmental functions of the MAPK proteins. MAPK-modules can be activated by various stimuli: mitogens (growth factors, cytokines), differentiation and stress factors (UV, osmolarity). The MAPK module consists of a *MAPKKK*, a *MAPKK* and a *MAPK*. Two MAPKs (ERK3 and ERK7) are not activated by an upstream MAPKK, but are constitutive active and are regulated by protein stability (indicated by an asterisk ∗). The MAPKs are subdivided into their corresponding subfamily, based on their dual phosphorylation domain (*dP-consensus*). The functions, obtained by gene-targeting or -silencing studies, but also immuno-histochemistry, are described for each MAPK. The lethality-index indicates if gene-disruption in mice resulted in a lethal developmental phenotype and at what day of development († = lethal, *No* = not lethal, *ND* = not determined). For erk3−/− mouse the results are not published yet. The indicated lethality shown for ERK3 (in white) is for MK5−/− mice, a direct target of ERK3.

interacts with the transcription factor myocyte enhancer factor 2 (MEF2).

Genetic studies with ERK5- or MEK5-deficient mice revealed that the MEK5–ERK5 pathway is essential for blood vessel development and cardiovascular development [35–40]. Mice that lack *erk5* or *mek5* die around E.10 due to defects in placental development, angiogenesis and cardiovascular development. Studies with conditional knockout, using the inducible promoter Mx1 to direct Cre expression, revealed that ablation of ERK5 in adult mice was lethal within 2–4 weeks after induction of the Cre recombinase [41]. Histological and in vitro analysis revealed that endothelial cells lost their integrity, became round and eventually apoptotic. The loss of these functional endothelial cells resulted in abnormally leaky blood vessels and hemorrhages in multiple organs. These findings indicate that survival of endothelial cells is MEK5 and ERK5 dependent, and that the cardiovascular defects observed in erk5−/− and mek5−/− embryos are due to the loss of endothelial cells [41].

In *Xenopus* knockdown of ERK5 by antisense morpholino injection inhibits neural differentiation and leads to growth retardation in the head and eventually to reduced head structures [36]. In this system the activation of the MEK5–ERK5 pathway is necessary for neural differentiation in early embryonic development. It is likely that the observed inhibition of neural differentiation may be one of the reasons for growth retardation in the head region.

Controversially, studies with conditional brain specific knockout mice, with Cre-expression controlled by the neuron specific synapsin I or nestin promoters revealed that these mice develop normally [37]. This might be due to species differential functions for ERK5, the use of an inappropriate promoter in the mouse model, or that a more global effect is responsible for the observed phenotypes in the brain after ERK5 knockdown in the *Xenopus*. Furthermore, expression of *erk5* is also mainly localized in the zebrafish brain and possibly a follow-up study in zebrafish will clarify developmental functions of ERK5 [33].

5. ERK7, ERK8 (MAPK15)

ERK7 (MAPK15) is found in rat, mouse and zebrafish and recently the *Dictyostelium erkB* (ERK2) has been characterized as an *erk7*-ortholog [42,43]. Genome-based analyses revealed that human *erk8* and rodent *erk7* are orthologs [44]. Furthermore, gene-predictions for *erk7* were found within the chicken and *Xenopus* genomes.

Like ERK3 and ERK5, the size of ERK7 and ERK8 is significantly larger than ERK1 and ERK2. Presumably, ERK7 is

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kept in a constitutively active conformation by its characteristic C-terminus [44]. Studies to determine their function in vertebrate development have not yet been reported.

6. JNK1,2,3 (MAPK9,10,11; SAPKγ,α,β)

Activated JNKs phosphorylate the N-terminus of the c-Jun protein and increases activity and stability of c-jun as a transcription factor [45,46]. Both JNK activation and c-Jun phosphorylation regulate cell growth, whereas sustained JNK and c-Jun activation following stress induces cell apoptosis, indicating that the role of JNK in cell survival and death is complex [47]. Mouse *jnk1* and *jnk2* are expressed ubiquitously during development, whereas *jnk3* is primarily expressed in the brain and to a lesser extent in the heart and testis. Mice lacking individual members of the *jnk* family are viable [48,49]. The *Jnk1*−/− knockout mice exhibited an affected T helper type-2 response, while T-cells from *jnk2*−/− mice showed impaired T helper type-1 differentiation. Both knockouts demonstrated defects in T cells activation and apoptosis of thymocytes [50]. Mice lacking both of the ubiquitously expressed *jnk* isoforms (*jnk1* and *jnk2*) die during mid-gastrulation (around E.7) with neural tube closure and brain defects [51]. Recently, it was shown that mice with a single allele of *jnk2* (*jnk1*−/− *jnk2*−/+), can survive to birth, but fail to close the optic fissure (retinal coloboma), a morphogenetic process that resembles dorsal and thorax closure in *Drosophila* by regulating BMP expression [52]. Localization of p-JNK in the spinal cord changes dramatically from cell-axons to the cell nuclei during development in the chicken, suggesting physiological functions of JNK during neuronal development [51]. In *Xenopus* oocytes initially two JNK isoforms, p40 JNK and p49 JNK, were shown [53], but until now only one *jnk*-gene (*jnk1*) is cloned in *Xenopus*. The ensemble genome project of *Xenopus tropicalis* does predict a *jnk3*-gene. JNK activity increases abruptly just prior to germinal vesicle breakdown and is shown to be involved in the non-canonical Wnt pathway to regulate *Xenopus* convergence and extension cell-movements [54]. Furthermore, the active JNK signaling complex formed by the scaffold protein POSH (Plenty of SH3s) and the JNK-module is essential for the expression of anterior neural genes and apoptosis in *Xenopus* anterior development [55]. In zebrafish also only one *jnk*-gene is described, which is expressed throughout development and shows distinct temporal and spatial expression patterns [33], but the latest release of the zebrafish genome (Zv6) predicts a second *jnk* gene (Fig. 2).

7. p38α,β,γ,δ (MAPK14,11,12,13)

The p38 family includes p38α (MAPK14, SAPK2a, CSBP), p38β (MAPK11, SAPK2b), p38γ (MAPK12, ERK6, SAPK3) and p38δ (MAPK12, SAPK4). Both *p38*α and *p38*β are widely expressed isoforms that are involved in regulation of cell proliferation, differentiation, development, and response to stress. The *p38*α knockout mice are lethal due to defects in placental angiogenesis [56,57]. In some genetic backgrounds, p38α deletion results in a decrease of erythropoietin (Epo) production, leading to anemia [58].

In *Xenopus*, the p38 MAPK signaling pathway is essential for skeletal muscle differentiation in tissue culture models. Knockdown of p38 MAPK causes distinct defects in myogenesis in *Xenopus laevis*, showing that p38 MAPK is involved in myogenesis during early development [59]. The zebrafish p38α otholog, p38a (MAPK14a), is asymmetrically activated on one side of the blastodisc during the early cleavage period in zebrafish embryos. The use of a dominant negative form of p38a revealed that asymmetric p38a activation is required for symmetric and synchronous cleavage, and may be regulated by the same machinery that controls the initiation of dorsalization signals [60].

By screening with the rat *erk3* gene, an *erk6*-clone was isolated from a human skeletal muscle cDNA library, that appeared to function as a signal transducer during differentiation of myoblasts to myotubes [61]. Later it was found that SAPK3 was identical to ERK6 [62,63]. Based on the phosphorylation domains and function, ERK6 is now classified as p38γ MAPK.

Mouse lacking p38β, p38γ or p38δ survive normally and do not show any obvious phenotypes [9,64,65]. Also the p38γ and p38δ double knockout mice was viable and fertile and had no obvious health problems [65]. Despite the suggested role for p38 MAPKs in inflammatory responses, these knockout mice do not show pathological changes, indicating dispensable physiological functions for p38β, p38γ and p38δ.

In frog, overexpression of a constitutively active mutant of the p38 activator MKK6 accelerates progesterone-induced maturation of *Xenopus* oocytes and was therefore suggested to be involved in the meiotic maturation. Phosphorylation of Cdc25C by p38γ/SAPK3 is important for the meiotic G2/M progression of *Xenopus* oocytes [66].

Information has been particularly limited regarding the functional role of p38δ (SAPK4). Eckert and coworkers describe p38δ as a regulator of surface epithelia differentiation and apoptosis [67]. Until now p38δ is found to be expressed in human, mouse and rat, but is not yet found in other vertebrates. However, a genome search in zebrafish (Zv6) and *Xenopus* (v38) does predict a possible *p38δ*-gene.

8. Conclusions and perspectives

There is an increased understanding about the different MAPK pathways and their crucial roles in vertebrate development. One of the striking observations is that some MAPKs (ERK3 and ERK7) are not regulated by the dogmatic MAPK module, but by protein stability. A major unresolved question is why such a variety of MAPKs is needed. Gene-disruption and -silencing experiments already showed central roles for most of these proteins. These approaches often resulted in early lethal effects, but also revealed redundancy (Fig. 3). The occurrence of redundancy can be addressed and overcome by targeting multiple genes at the same time. Also further conditional and tissue specific gene-targeting experiments will help to understand the functions of the different MAPKs. The use of different vertebrate model organisms and their specific beneficial characteristics will be helpful to achieve this goal. The recent characterization of the zebrafish *mapk* gene-family [33] and its advantage to study early embryogenesis ex utero provides an excellent system for further investigation of the functions of MAPKs in early development in vivo. The transparency of zebrafish embryos is of particular advantage to explore the link of MAPKs to cell migration processes. This

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has already resulted in the identification of the role for ERK2 in developmental cell migration, additive to the well established proliferation and differentiation functions.

Acknowledgements: We apologize to our colleagues, whose work could not be cited because of space constraints.

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