# The Mitogen-Activated Protein Kinase Signaling Cascade: From Bench to Bedside

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Over the past decade several related intracellular signaling pathways, collectively known as mitogen-activated protein kinase (MAPK) signaling cascades, have been elucidated [1–3]. These cascades play a key role in the transmission of extracellular signals to their intracellular targets and thus initiate cellular processes such as proliferation, differentiation, development, stress response, and apoptosis. Each of these signaling cascades consists of three to six tiers of protein kinases that sequentially activate each other by phosphorylation. Four distinct MAPK cascades are currently known and are named according to the subgroup of their MAPK components [Figure 1]:

- The extracellular signal-regulated kinase (ERK) cascade, which was the first MAPK cascade elucidated and is the subject of this review.
- The Jun N-terminal kinase (JNK) cascade, also known as stress-activated protein kinase 1 (SAPK1), is activated by various types of cellular stresses including the inflammatory cytokines tumor necrosis factor-alpha and interleukin-1, osmolar stress and shear stress, but also by hormones and growth factors.
- The p38MAPK cascade is another stress-activated MAPK cascade and is therefore known as SAPK2-4.
- The Big MAPK (BMK also known as ERK5) cascade is the fourth MAPK cascade, so called due to the size of BMK, 110 kDa, compared to 40–45 kDa of the other MAPKs. The BMK is activated by oxidative stress and hyperosmolarity as well as by mitogens such as serum and growth factors.

This review will focus on the ERK cascade and is composed of two parts. In the first part we describe the components of the ERK cascade, its activation and regulation [Figure 2]. In the second part we review the current knowledge on the involvement of the ERK cascade in various disease processes and its potential role as a target for the development of new medications.

## The ERK cascade

The ERK cascade is activated by a large variety of extracellular agents, such as growth factors, hormones and neurotransmitters. Epidermal growth factor, platelet-derived growth factor, fibroblast growth factor, neurite growth factor, angiotensin II, endothelin, thrombin, thromboxane A2 and norepinephrine are just a few of the known activators of the ERK cascade. While growth factors activate the ERK cascade through receptor tyrosine kinases, hormones and cytokines usually activate the ERK cascade through G-protein-coupled receptors (GPCR). Both pathways lead to the activation of Raf kinases, the MAPK kinase kinase (MAP3K) of the cascade, which in turn activate MAPK/ERK kinases (MEKs), the MAPK kinase (MAPKK) of the cascade, which then activate the ERKs. The activated ERKs are able to phosphorylate cytosolic substrates such as RSKs and cytosolic phospholipase A2 (cPLA2), the rate-limiting enzyme in pathways involving arachidonic acid release. In the nucleus, the ERKs can phosphorylate the transcription factor Elk-1 and transcription modulators, such as Ets1, Ets2, Ets transrepressors, Stats and estrogen receptor [1,3].

### Activation of the ERK cascade

- ***Activation by receptor tyrosine kinases***

Activation of a receptor tyrosine kinase by an appropriate ligand leads to dimerization and autophosphorylation of the receptor. Adapter molecules such as Grb2, which contains SH2 domain, bind to the activated receptor and recruit to the membrane a guanine nucleotide exchange protein (e.g., Sos). This enzyme in turn activates the membranal form of the small G-protein Ras by exchanging its GDP by GTP. Ras-GTP binds to Raf-1, bringing it to the plasma membrane where it is activated and further initiates the rest of the ERK cascade [1,3].

- ***Activation by G protein-coupled receptor* (GPCR)**

The G proteins are composed of three subunits: $\alpha$, $\beta$ and $\gamma$. Stimulation of a GPCR leads to the exchange of GDP by GTP on the G$\alpha$ subunit leading to its dissociation from the G$\beta\gamma$ subunits. All four subtypes of G$\alpha$ (G$\alpha$s, G$\alpha$q, G$\alpha$i, G$\alpha$12), as well as the dissociated G$\beta\gamma$ dimer and other interacting proteins, can modulate the activity of the ERK pathway. Several mechanisms are involved in this modulation in different cell types. For example, the G$\alpha$s subunit stimulates the activity of adenylyl cyclase, which produces cAMP. The cAMP then activates the cAMP-dependent protein kinase (PKA), which can either inhibit or activate the ERK cascade by several mechanisms. In addition, cAMP can stimulate a specific exchange factor, Epac, which can activate Raf and thereby the rest of the cascade. Other pathways that connect G proteins to ERK are transactivation of receptor tyrosine kinases by Gi, activation of PKC and guinine nucleotide exchange factors (GEFs) by Gq, and activation of c-Src by several GPCR/G protein components [2].

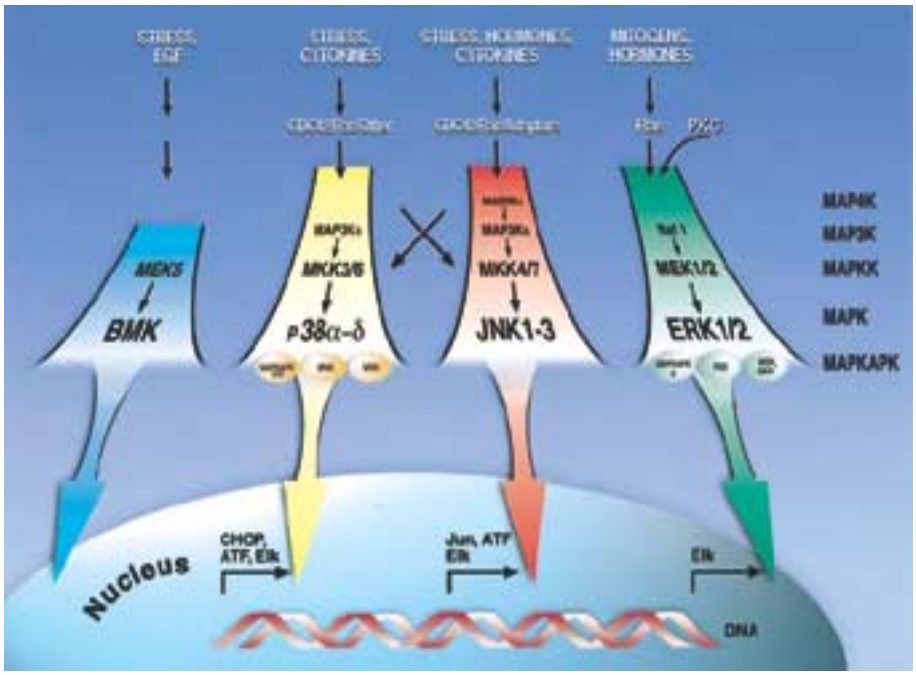


**Figure 1.** Schematic representation of the MAP kinase signaling cascades. Four distinct MAPK cascades are currently known and are named according to the subgroup of their MAPK components: the extracellular signal-regulated kinase (ERK) cascade, the Jun N-terminal kinase (JNK) cascade, the p38MAPK cascade, and the Big MAPK (BMK) cascade. Each of these signaling cascades consists of three to six tiers of protein kinases that sequentially activate each other by phosphorylation.

**Properties of the main components of the ERK cascade**

- ***The structure of Ras***

The Ras family consists of three small GTPases of 21 kDa: H-Ras, N-Ras and K-Ras [4]. As mentioned, Ras proteins are activated by exchange factors, and activated Ras can activate Raf, PI3 kinase and Ran. Ras proteins cycle between an active GTP-bound state and an inactive GDP-bound state. Activation of GEFS (e.g., Sos) leads to the dissociation of GDP from Ras. The free Ras rapidly associates with GTP and thus becomes active. The active Ras slowly converts the GTP to GDP via intrinsic GTPase activity and this reaction is enhanced by RAS-GTPASE-activating protein (RAS-GAP), which is responsible for the rapid inactivation of Ras. Constitutive activation of Ras is an important factor in the malignant growth of cancer cells, and mutations in the Ras proto-oncogene are found in about 30% of all human tumors. Most of these mutations prevent the GTPase action on Ras, leading to the latter's constitutive activation. The Ras proteins are produced as precursor proteins that require several post-translational modifications to acquire full biologic activity. Two of these modifications are farnesylation and palmitoylation, which enhance the affinity of Ras to the plasma membrane and thus its ability to activate Raf-1. Since the post-translational modification by the enzyme Ras farnesyltransferase is specific to Ras, inhibitors of this enzyme can serve as a novel therapy for human malignancies.

- ***The structure of Raf kinases***

The Raf family of protein kinases is composed of three isoforms: Raf-1 (74 kDa), A-Raf (68 kDa) and B-Raf (95 kDa), of which Raf-1 is the best studied [1,3]. The Raf kinases contain three conserved regions, termed CR1, CR2 and CR3. CR1 and CR2 are important for the regulation of the catalytic kinase domain, located in CR3. Raf-1 also contains a phosphatidic acid domain that might be important in its mode of activation. The regulation of Raf-1 is complex and involves changes of cellular localization, phosphorylation by multiple protein kinases (e.g., Src, AKT, PKC), and interactions with regulatory proteins (e.g., 14-3-3, SUR-8). Activating mutations in Raf-1 involve deletion of its CR1 and CR2 domains, leaving a free unregulated kinase that can be found in human tumors. This makes Raf-1 another target for the development of anticancer therapy.

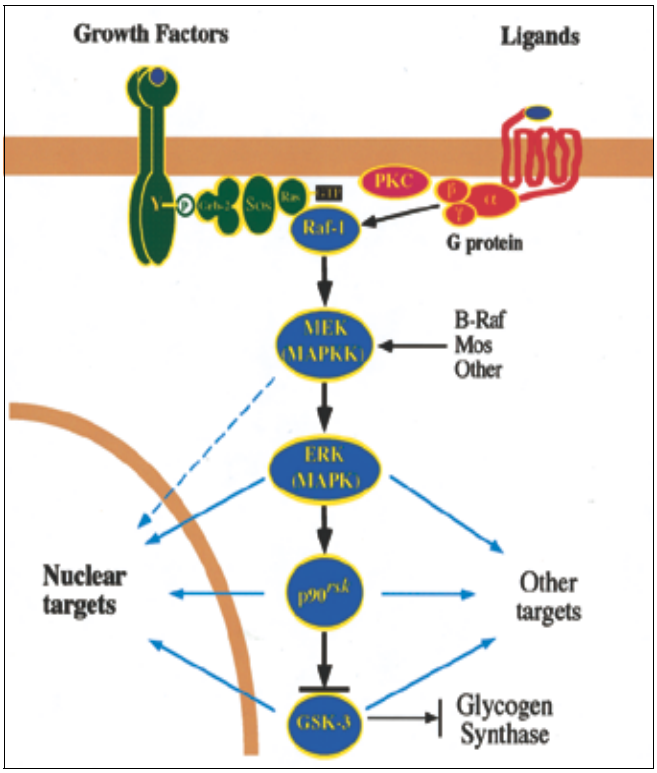


**Figure 2.** Schematic representation of the ERK signaling cascade. Extracellular signals can activate the ERK cascade through activation of either receptor tyrosine kinases or G-protein-coupled receptors. Both pathways lead to the activation of Raf kinases, which in turn activate MAPK/ERK kinases (MEKs), which then activate ERKs. The activated ERKs are able to phosphorylate cytosolic substrates or translocate to the nucleus and phosphorylate transcription factors.

- ***The structure of* MEK**

There are three members in the MEK family: MEK1 (45 kDa), MEK2 (46 kDa) and MEK1b (43 kDa); the latter does not have ERK-activating activity [1,3]. The activation of MEKs by their upstream stimulators involves protein phosphorylation on two serine residues located in the characteristic Ser-Xaa-Ala-Xaa-Ser motif within the activation loop. MEKs are highly specific towards the downstream components ERK1, ERK1b and ERK2 and thus confer the specificity of the ERK cascade. The MEKs are able to phosphorylate both regulatory residues Thr and Tyr of ERKs and thus belong to the small family of the regulatory dual-specificity protein kinases.

- ***The structure of* ERK**

Three protein kinases were reported to exist in this extensively studied group of MAPKs; namely ERK1 ($p44^{MAPK}$), ERK2 ($p42^{MAPK}$), and an alternative spliced form of ERK1 (the 46 kDa ERK1b) [1,5]. Because of the high degree of similarity between ERK1, ERK1b and ERK2, they are usually considered to be functionally redundant, although some differences in their specificity have nonetheless been reported. Common to this group is the motif Thr-Glu-Tyr, located in a surface loop called the activation lip. Phosphorylation of both Thr 183 and Tyr 185 residues in this region is required for the activation of the enzyme, and the only upstream mechanism leading to the activation of ERKs is the phosphorylation of these residues by MEKs. Studies of the three-dimensional structure of unphosphorylated and phosphorylated ERK2 revealed that, like other protein kinases, ERK2 consists of a smaller N-terminal domain and a larger C-terminal domain connected by a linker region. ATP binds to a deep pocket at the interface of the two domains, and protein substrates bind on the surface of the pocket. The activation loop lies at the mouth of the active site. In the low activity state, unphosphorylated Tyr 185 partially blocks the protein substrate-binding site. Upon activation, phosphorylated Tyr and Thr residues bind to an anion-binding pocket and help to form the binding surface for the protein substrate. These changes induce full catalytic activity (~5 μmol/min/mg) of ERK2, which is about 5 orders of magnitude higher than its basal activity. The ERKs are "proline-directed" protein kinases, meaning that they phosphorylate Ser or Thr residues that are neighbors of prolines. This rather broad nature of substrate recognition enables ERKs to phosphorylate numerous proteins.

- ***Subcellular localization of the components of the* ERK *cascade***

Among the key steps in the signaling mechanism of MAPK cascades are changes in subcellular localization of their components [1,3]. In resting cells, most of the kinases of the ERK cascade are localized to the cytosol. However, upon stimulation, most of the kinases change their subcellular localization. Thus, Raf-1 translocates to the plasma membrane, whereas the kinases downstream of Raf-1, namely MEKs, ERKs and RSKs, translocate into the nucleus. While MEKs are rapidly exported from the nucleus soon after their translocation, ERKs and RSKs are retained in the nucleus for longer times after stimulation. The proper subcellular localization of the various components plays an important role in regulating the physiologic functions of the ERK cascade. Prevention of nuclear localization of constitutively active MEK1/2 reduces its oncogenic potential, and nuclear localization of ERKs has been correlated with mitogenesis. Moreover, prevention of the nuclear translocation of ERKs strongly inhibits gene transcription. Thus, a better understanding of the mechanisms involved in the control of this important step may lead to the development of translocation inhibitors to treat various disease states. The mechanisms involved in the regulation of subcellular localization of the ERKs were studied extensively in recent years. In resting cells, both ERK1 and ERK2 are localized in the cytosol. Upon stimulation, as much as 85% of ERK molecules appear to dissociate from their cytosolic anchors and translocate into the nucleus. This translocation is rapid (seen in 5 minutes), reversible, and may involve two distinct mechanisms of nuclear import: one is a passive non-regulated mechanism, the other a faster active process. The translocated ERKs accumulate in the nucleus where a large amount of ERKs can be observed even after their activity has declined. ERK retention in the cytosol is MEK-dependent, and recently our group identified a primary sequence important for this retention of ERKs, termed cytosolic retention sequence (CRS, amino acids 312-320 of ERK2) [6]. We also found that the nuclear translocation of ERK2 is regulated mainly through a stimulation-induced dissociation from its cytosolic anchoring due to conformational change in the activation loop [7].

- ***Inactivation of the* ERKs**

Another regulatory step in the activity of the ERK cascade is its inactivation. As dual phosphorylation on Thr and Tyr is required to activate a MAPK, both Ser/Thr protein phosphatases (e.g., PP2A) and protein Tyr-phosphatases can efficiently inactivate MAPKs. An important subclass of the protein Tyr-phosphatases possesses the ability to dephosphorylate both phosphoTyr and phosphoThr, and are therefore termed dual-specificity phosphatases [8]. MAPK phosphatases (MKPs), which appear to be selective for both regulatory residues in MAPKs, are important constituents in this subclass of phosphatases. To date, at least nine members of this subgroup have been identified; all are inducible proteins. Stimulation by growth factors, cytokines or cellular stress leads to a rapid transcription of the MKPs, which then translocate to a specific cellular compartment where they inactivate MAPKs and prevent, by direct interaction, further activation of inactive MAPK molecules. The various MKPs differ in their tissue distribution, subcellular localization and specificity toward different MAPKs. For example, MKP1 is mainly nuclear and can dephosphorylate p38 MAPK>JNK>>ERK, whereas MKP-3 is cytosolic and is highly selective for ERKs. The distinct distribution and specificity of the various MKPs enables them to play a major role in the regulation of the MAPK cascades.

## The ERK cascade in physiologic processes

Although the activation of the ERK cascade was initially implicated in the transmission and control of mitogenic signals, it is now

known that this cascade plays an important role in many physiologic processes, including differentiation, development, stress response, learning and memory processes in the brain, and morphology determination. The involvement of the ERK cascade in some of these processes is discussed below.

#### ERKs in proliferation and mitogenic transformation

The rapid activation of MEKs and ERKs in response to mitogens in various cell lines has implicated these protein kinases in the control of cell proliferation. Indeed, the ERK cascade has been directly implicated in the induction of proliferation and in oncogenic transformation [1,3]. A convincing line of evidence for the involvement of the ERK cascade in proliferation was achieved by using constitutively active and dominant negative forms of MEK1. While the dominant negative form of MEK1 reduced the rate of proliferation, the constitutively activated form accelerated it. The ERK cascade can influence cell growth and proliferation by participating in many of the cell cycle control mechanisms [9]. For example, activation of the ERK cascade by growth factors promotes expression of cyclin D in early stages of the G1 phase of the cell cycle. It also promotes the assembly of cyclin D-cyclin dependent kinase 4/6 (CDK4/6) kinase complexes. This occurs through upregulation of p21waf1/Cip1, which was shown to allow progression through the G1 restriction point. In addition, activation of the ERK cascades promotes the degradation of the CDK inhibitor p27Kip1 and therefore allows the release of active cyclin E-CDK2 and entry into the S-phase.

#### ERKs in development and differentiation

Another physiologic response regulated through the ERK cascade is cellular differentiation. Different members of the ERK cascade have been implicated in processes such as monocytic differentiation, neurite outgrowth of PC12 cells, T cell maturation, and mast cell development. Since ERKs are activated in somatic cells in response to many extracellular stimuli, it is not surprising that ERK is also involved in developmental processes requiring the proliferation of a new group of cells when new organs develop in growing organisms. Indeed, such involvement has been clearly demonstrated in several developmental systems such as in *Drosophila* embryogenesis, *Xenopus* embryogenesis and in *C. elegans* vulval development [1,3].

#### ERKs in learning and memory

Activation of ERK1 and ERK2 has also been implicated in synaptic plasticity and other processes that allow consolidation of memory in the brain. Processes of learning and memory in mammalian brains involve the establishment of new synaptic connections regulated by several intracellular signaling pathways. The involvement of ERKs in learning has been demonstrated in *Aplisia* as well as in several model systems such as taste learning, fear conditioning and the acquisition of memory. Activation of ERK in rat insular cortex was found to be necessary for the encoding of long-term but not short-term memory. Moreover, the activation of ERK was recently discovered to play an important role in the acquisition of memory but not in its retrieval [10].

#### ERKs in apoptosis

In addition to its roles in proliferation and cell cycle control, the ERK cascade has been implicated in the control of apoptosis. In most cell types and conditions the ERK cascade seems to have an anti-apoptotic effect, and a reduction in its activity is essential for the process of apoptosis to proceed. Thus, upon serum starvation of PC12 cells, ERK activity is reduced and thus allows apoptosis to occur. The protection from apoptosis could be due to interference of components of the ERK cascade in the apoptotic machinery. For example, upon activation Raf-1 is involved in the phosphorylation of the mitochondrial protein Bad, thus preventing its interaction with Bcl-2 and inhibiting its mediated apoptosis. The Raf-1-induced protection from apoptosis involves activation of MEK, ERK and RSK [1,3]. Interestingly, the ERK cascade, as well as the p38MAPK cascade, plays a role in taxol-induced apoptosis. Therefore, although a rare event, the ERK cascade may be involved in the onset of apoptosis in some cellular systems.

#### *In vivo* analysis of MEK and ERK function

An important step in our understanding of the function of proteins in the whole animal is the use of gene disruption experiments. To date, only knockouts of ERK1 and MEK1 have been described. The knockout of ERK1 resulted only in a modest defect in T cell development, probably because most ERK1 functions can be performed by ERK2. On the other hand, a marked defect was found in the MEK1$^{-/-}$ mice. These mice die *in utero*, exhibiting defective placental vascularization [11]. It is likely that in the future the transgenic mice technique will provide much more information on the role of the ERK cascade in various tissues and organs.

The *in vivo* activation of the ERK cascade can be monitored by examination of the *in situ* distribution of the active form of ERK using a specific monoclonal antibody. Such antibodies were developed by our group and were proven suitable for immunofluorescence staining in a wide variety of organisms. For example, these antibodies were used for the elucidation of the *in situ* activation pattern of *Drosophila* EGF receptor pathway during development.

## The ERK cascade in the pathogenesis of human diseases

In the last few years, laboratories all over the world have been trying to elucidate the role of the MAP kinase cascades and the ERK cascade in particular, in pathologic processes, especially those involving proliferation. Although the detection of ERK activation is fairly simple, interpretation of these studies mandates caution. One should bear in mind that the ERK cascade participates in various ways in many physiologic processes, thus making it hard to discern its exact role in disease states. In this section we describe some of the main studies demonstrating a role of the ERK cascade and specifically of ERKs in several disease states.

#### ERK and malignancy

The involvement of the ERK cascade in human malignancies has been studied extensively. The activation of the ERK cascade plays a

major role in malignant transformation, and upstream components of the cascade, including the three isoforms of Ras and Raf-1, are well known oncogenes. While no mutations of ERK have yet been identified in human malignant diseases, its activation was demonstrated in several neoplasms. The most comprehensive screen of ERK activation in human tumors was done by Hoshino et al. [12]. A small constitutive activation of ERKs, which was about 50% above basal activity, was found in 50 of 138 human tumor *cell lines* screened, and in particular in cells derived from colon, lung, kidney, ovary and pancreas tissue but not in tissues of brain, liver, stomach and hematopoietic origin. Similar small activation of the ERKs was also found in 23 of 102 human *primary tumors* screened: 11 of 34 lung cancer samples, 7 of 34 colon cancer and 5 of 11 renal cell carcinomas, but not in 23 cases of hepatocellular carcinoma.

Activation of ERK in human malignancies was reported by other groups as well:

- *Breast cancer.* Increased activation and/or expression was found in several studies. Sivaraman and colleagues [13] observed increased activation of ERKs in 11 patients but not in 26 healthy control subjects. Similar findings were reported by Maemura et al. [14]. In a large recent study, Mueller et al. [15] reported on elevated ERK activity in 131 tissue samples from primary breast tumors when compared to 18 normal tissues adjacent to tumors. In this group higher activity of ERKs was found to be a bad prognostic sign, correlated to spread as well as to relapse of the disease [15].
- *Colon cancer.* The results regarding activation of ERKs in colon cancer are contradictory. While several studies found increased activation of ERKs in colorectal specimens [12,16,17], three other groups reported a *reduction* in ERK activity in colorectal specimens of 63 patients [18–20].
- *Acute leukemia*. Constitutive MEKs and ERKs activation is found in up to 70% of patients suffering from acute, but not chronic, leukemia [21,22]. Interestingly, Kim et al. [22] related ERK activation to a combination of activation of MEKs, overexpression of ERKs and downregulation of the MAPK phosphatase PAC1.
- *Prostate carcinoma*. Gioeli et al. [23] used immunohistochemistry methods to detect nuclear localization of ERKs as a measure of ERK activation in prostate cancer specimens. Nuclear translocation of ERKs was found in 19 of 60 primary tumors and in 8 of 18 metastatic tumors. A positive correlation was found between the translocation of ERKs and the clinical stage of the disease [23].
- *Renal cell carcinoma*. Activation of ERKs was found in 12 of 25 patients and the degree of activation correlated to the spread of the tumor [24].

It is of note, however, that in most of these studies ERK was considered constitutively active in primary tumors when its activity was only 1.5 to 2 times higher than a matched non-tumorous tissue. Moreover, in several primary tumors tested, ERK activity was normal despite the presence of oncogenic (activated) Ras or Raf, which should constantly activate the ERK cascade. On the other hand, when tested in cell lines, stimulation of cells by mitogenic agents resulted in a 20–100 fold increase in the activity of ERKs' basal activity. This difference between cell lines and primary tumors can be explained by the activity of phosphatases that are upregulated upon stimulation and reduce ERK activity in tumorous tissue.

### ERK and the cardiovascular system

Cardiac hypertrophy is a physiologic process of adaptation that, under certain conditions, can lead to heart failure. Mechanical stress, growth factors and hormones such as epidermal growth factor, endothelin-1, angiotensin II and norepinephrine are all involved in cardiac hypertrophy. All these factors are able to activate the ERK cascade, which seems to play a major role in the process of cardiac hypertrophy [25]. An *in vivo* association between ERK, angiotensin-converting enzyme (ACE) and heart disease was found in a study by Goette et al. [26]. In this work, increased expression and activation of ERKs as well as increased expression of ACE were observed in atrial biopsies taken during open heart surgery from 25 patients with atrial fibrillation as compared to a control group. The activation of ERKs was reduced in patients treated with ACE inhibitors, thus establishing the link between angiotensin II and ERK. Recently, activation of ERKs was found in atrial tissue samples taken at different stages of open heart surgery. The activation occurred following ischemia and even more following reperfusion. However, the exact role of the cascade in ischemia and reperfusion is yet to be defined [27].

### ERK in other disease states

In addition to the above processes the ERK cascade is known to be involved in several physiologic and pathologic processes. Examples of the physiologic roles are the regulation of hormone action including gonadotropin-releasing hormone (GnRH) [2] and the thyroid hormone [28], as well as the involvement of ERK in repair of gastric ulcers [29]. Examples of the pathologic processes are:

- *Diabetes mellitus*. ERK is activated by insulin as well as directly by hyperglycemia. The ERK cascade is also implicated in many of the disease's complications [30,31].
- *Osteoarthritis.* Activation of the cascade was found in synovial tissue from rheumatoid arthritis but not from osteoarthritis patients [32].
- *Asthma.* ERK activation is involved in the proliferation of airway smooth muscles in asthma [33].
- *Stroke.* ERK was recently found to be activated in human brain following acute ischemic stroke [34].
- *Influenza*. Interestingly, the ERK cascade was recently found to be necessary for the propagation of influenza virus; and U0126, a MEK inhibitor, was found to inhibit the propagation of this virus *in vitro* [35].

### The ERK cascade as a potential target for novel therapies

The activation of the ERK cascade in so many disease states, particularly human malignancies, makes it a potential target for new drugs. Specific approaches for the inhibition of upstream components of the ERK cascade are now being tested and are entering clinical use. Inhibition of the cascade at the receptor level is the mechanism of action of the humanized antibody trastuzumab

(Herceptin), which blocks the ErbB2 receptor. Trastuzumab is now in clinical use for the treatment of advanced breast cancer and was recently proven effective in a large phase 3 clinical trial [36]. Inhibition of Ras activity can be accomplished by inhibition of the enzyme Ras farnesyltransferase. Numerous such inhibitors are currently known; most of them are chemically synthesized small molecules and some are currently being tested in several phase 1 and 2 clinical trials [4]. Another target for anticancer therapy is Raf-1. Raf-1 can be downregulated by the use of an antisense oligonucleotide that prevents the translation of Raf-1 mRNA. Such an antisense was tested in a phase 1 study and was found to be well tolerated and effective in 34 patients with solid tumors refractory to standard therapy [37]. Direct inhibition of MEK can serve as another novel therapeutic modality. Several inhibitors of MEK are in routine laboratory use. Recently, Sebolt-Leopold et al. [38] discovered a new MEK inhibitor, PD 184352, which was found to inhibit the growth of colon carcinoma of mouse or human origin implanted in mice, even when given orally. Importantly, no signs of toxicity were seen in the treated mice. This inhibitor is presently being tested in a phase 2 trial.

Another class of drugs, now known to exert at least some of their effects through the ERK cascade, is non-steroidal anti-inflammatory drugs (NSAIDS). While the main mechanism of action of NSAIDS is blocking prostaglandin synthesis by the enzymes cyclooxygenase 1 and 2 (COX-1/2), these drugs were recently found to inhibit angiogenesis and induce apoptosis through inhibition of ERK1/2 activity [39,40]. This suggests that at least some of the effects of these drugs in the prevention of colon cancer, as well as some of their effects on preventing ulcer healing, are mediated through the ERK cascade. Interestingly the effects of these drugs do not depend upon COX-1 or COX-2 selectivity [39].

Despite these encouraging developments, one must remember that since the activation of ERKs occurs in so many physiologic processes, which obviously must not be inhibited, its inhibition in a non-specific manner might be harmful and thus prevent the clinical use of ERK cascade inhibitors.

## Conclusion

The ERK cascade, known for less than a decade, is implicated in many physiologic processes such as proliferation, differentiation, development, stress response, and apoptosis. Recent studies have revealed the significance of the ERK cascade in pathologic processes such as malignant transformation, cardiac hypertrophy and endocrine disorders. Exploring the role of the ERK cascade in pathologic states may lead not only to a better understanding of these states but also to the development of new classes of medications.

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