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MAP'ing CNS Development and Cognition: An ERKsome Process

Ivy S. Samuels[1,2,3], **Sulagna C. Saitta**[4], and **Gary E. Landreth**[1,*]

[1]Department of Neurosciences, Case Western Reserve University, Cleveland, OH 44106, USA

[2]Department of Ophthalmic Research, Cole Eye Institute, Cleveland, OH 44195, USA

[3]Louis Stokes Cleveland VA Medical Center, Cleveland, OH 44106, USA

[4]Children's Hospital of Philadelphia, University of Pennsylvania, Philadelphia, PA 19104, USA

Abstract

The ERK MAP kinase signaling cascade plays critical roles in brain development, learning, memory, and cognition. It has recently been appreciated that mutation or deletion of elements within this signaling pathway leads to developmental syndromes in humans that are associated with impaired cognitive function and autism. Here, we review recent studies that provide insight into the biological roles of the ERKs in the brain that may underlie the cognitive deficits seen in these syndromes.

The extracellular signal regulated kinase (ERK) subfamily of mitogen-activated protein (MAP) kinases comprises the central elements of one of the most important and best-studied intracellular signaling pathways (Rubinfeld and Seger, 2005). This pathway mediates the transmission of signals from cell surface receptors to cytoplasmic and nuclear effectors. Indeed, the ERKs are activated in response to extracellular stimuli that target a broad array of receptors (Rubinfeld and Seger, 2005). These receptors are physically and functionally linked to the ERK cascade through a diverse group of molecular adapters that couple them to activation of the GTPases of the Ras family, Ras and Rap1 (Figure 1). Ligand binding results in the conversion of Ras-related GTPases into an active conformation, enabling them to interact with and promote the activation of the raf kinases, which initiate downstream signaling through the ERK cascade. The core elements of the ERK signaling pathway comprise a three-tiered protein kinase cascade including the raf kinases (B-Raf and Raf1) that phosphorylate and activate the MAP kinase kinases, MEK1/2, which in turn activate ERK1/2 (Rubinfeld and Seger, 2005). The ERKs phosphorylate a host of proteins and activate other protein kinases (RSK1–4, MSK1/2, MNK1/2) that are responsible for the regulation of transcription and translation. The ERKs and their immediate targets, the RSKs, are translocated into the nucleus upon activation, allowing the phosphorylation of transcription factors that mediate the direct regulation of gene expression.

ERK1/2 share 84% sequence identity but little is known about their isoform-specific actions. Both isoforms are ubiquitously expressed, are coordinately activated, and have identical substrate specificity. The relative expression of ERK2 is greater than that of ERK1, although both are expressed throughout the adult brain. The ERKs are most highly expressed in neurons, compared to all other cell types.

*Correspondence: gel2@case.edu.

In the nervous system, the ERKs are involved in processes as diverse as the genesis of neural progenitors, learning, and memory. During development the ERKs respond principally to growth factors through the activation of receptor tyrosine kinases. In the mature nervous system, the ERKs are activated in neurons in response to synaptic activity (Davis and Laroche, 2006). Recently, mutations within elements of the ERK signaling cascade have been associated with a number of clinical syndromes that have been collectively termed “neuro-cardio-facial-cutaneous (NCFC) syndromes” (Bentires-Alj et al., 2006). Change in gene copy number of ERK signaling elements has also been described for other clinical phenotypes. New studies have identified individuals with microdeletions encompassing the *MAPK1* gene that encodes ERK2 in distal chromosome 22q11 who exhibit cognitive deficits and features of the Di-George syndrome (DGS) spectrum (Shaikh et al., 2007). Further, a deletion of a locus on chromosome 16 that includes the *MAPK3* gene encoding ERK1 has been associated with autism and craniofacial anomalies (Kumar et al., 2008; Weiss et al., 2008). These syndromes frequently include CNS developmental abnormalities and functional deficits. Collectively, these findings suggest that genetic alterations involving elements of the ERK signaling cascade are a significant cause of neurodevelopmental and cognitive disorders. A number of recent studies have shed new light on the actions of the ERKs both in neural development and in the mature brain, providing insight into the biological basis of the deficits observed in humans in which signaling through the ERK pathway has been perturbed.

Clinical Syndromes Associated with Altered ERK Signaling

NCFC Syndromes

A group of related syndromes are characterized by cardiac and craniofacial abnormalities and include Costello, Noonan, LEOPARD, and cardio-facio-cutaneous (CFC) syndromes. It has recently been recognized that the mutated genes act within a common genetic pathway regulating ERK activation (Figure 1) (Aoki et al., 2008; Denayer et al., 2008). Importantly, similar phenotypes arise from both gain of function and loss of function of a single allele of elements of the ERK pathway (Table 1). Individuals with mutations associated with these syndromes can have cardiac defects including pulmonic valve stenosis, arrhythmia, and cardiomyopathy. While the cardiac and craniofacial defects in these disorders have been well documented, the CNS manifestations of these disorders have not been extensively studied and less is known about the developmental basis of this part of the phenotype. Noonan syndrome (NS) results from point mutations in genes encoding upstream elements of the ERK cascade, namely SHP2, K-Ras, SOS1, and Raf1 (Gelb and Tartaglia, 2006). This syndrome is phenotypically diverse, and can include developmental delays and behavioral and learning disabilities (Lee et al., 2005). Mental retardation is reported in approximately 25% of patients (Yoshida et al., 2004), but normal cognitive development is reported as well (Tartaglia et al., 2002). Classical features include pulmonic stenosis, short stature, and facial dysmorphia. Approximately half of individuals with NS show gain-of-function mutations in the *PTPN11* gene, which encodes SHP2 (Tartaglia et al., 2002). SHP2 plays critical roles in fibroblast growth factor receptor (FGFR) and Trk signaling to the ERKs. Germline mutations in *SOS1* have been found in approximately 10% of NS patients, while *RAF1* and *K-RAS* account for about 4%–15% and 1%–2% of mutations, respectively. LEOPARD syndrome (lentigines, EKG abnormalities, ocular hypertelorism, pulmonic stenosis, abnormal genitalia, retardation of growth, and deafness) arises from loss-of-function mutations in *PTPN11* and *K-RAS* that are distinct from those associated with NS, though there is clinical overlap between the two disorders (Bentires-Alj et al., 2006). Two recent reports of gain-of-function mutations in *RAF1* were shown to cause Noonan and LEOPARD syndromes, and were associated with increased ERK activation (Pandit et al., 2007; Razzaque et al., 2007). CFC has recently been linked to mutations in K-Ras, B-Raf, and MEK1/2 (Roberts et al., 2006). In CFC syndrome, mental retardation and developmental

delay is found in over 80% of cases. These patients exhibit structural CNS anomalies, most prominently reduced cerebral volume and hypoplasia of the frontal lobe and cerebellum. Costello syndrome is associated with activating mutations of H-RAS and has a clinical profile similar to CFC (Rauen, 2007; Roberts et al., 2006). The neurological manifestations of Costello syndrome include frontal lobe atrophy (40% of patients), cerebellar abnormalities (26% of patients), and significant mental retardation (Delrue et al., 2003).

Neurofibromatosis type 1 (NF1) arises from mutation or deletion of the *NF1* gene encoding neurofibromin, a Ras GTPase activating protein that acts as a negative regulator of ERK activation (Ferner, 2007). Over half of individuals with *NF1* mutations have intellectual impairment. Individuals with deletions encompassing the *NF1* gene exhibit a more severe phenotype and more profound intellectual impairment (Descheemaeker et al., 2004) with craniofacial abnormalities (Leppig et al., 1997). The bases of the impaired neurocognitive functions have been argued to arise from defects in corticogenesis. NF1 is associated with macrocephaly, and murine models with analogous *NF1* mutations or deletions exhibit increased proliferation of neural progenitors during embryogenesis that are correlated with ERK activation (Hegedus et al., 2007). However, recent work by Cui et al. (2008) have demonstrated an ongoing requirement for neuronal NF1 and ERK activity in long-term potentiation (LTP), learning, and memory. They reported that loss of NF1 is associated with an enhancement of ERK-dependent GABA release, which contributes to cognitive impairment in murine models of this disorder.

Recently a new syndrome with a similar clinical presentation has been described, termed NF1-like syndrome, which results from loss-of-function mutations in the *SPRED1* gene. The *SPRED1* gene product normally acts to suppress ERK activation, as does NF1 (Brems et al., 2007). Thus, loss-of-function mutations in *NF1* or *SPRED1* result in elevation of ERK pathway activation. These individuals are also cognitively impaired and macrocephalic and exhibit facial dysmorphism similar to other NCFC syndromes.

In addition, two genes that are direct targets of the ERK cascade are associated with X-linked mental retardation. Coffin-Lowry syndrome results from mutations at Xp22.2, resulting in loss of function of RSK2 that is associated with severe mental retardation (Yntema et al., 1999). Similarly, deletions at Xq21 that include the *RSK4* gene result in a similar phenotype with profound cognitive impairment (Shalin et al., 2006).

DGS (22q11 Deletion syndrome) is the most common (1/3000) microdeletion syndrome in humans. DGS is most frequently associated with loss of a 3 Mb region in chromosome 22q11 (Lindsay, 2001; Scambler, 2000) and has clinical features distinct from the NCFC disease spectrum. DGS is characterized by conotruncal cardiac defects and craniofacial anomalies that may arise from the combinatorial effects of deleting multiple (330) genes. Importantly, two genes (*TBX1* and *CRKL*) that are both deleted in the common 3 Mb deletion of DGS act within a genetic pathway that regulates ERK1/2 signaling in neural crest cells (Frank et al., 2002; Guris et al., 2006; Moon et al., 2006). *TBX1* acts to regulate FGF8 expression (Wurdak et al., 2006), and CRKL is an adaptor protein linking the FGFRs (and Trk receptors) to the ERK cascade (Figure 1). The neurological features of DGS have been less intensively studied until recently (Antshel et al., 2005; Schaer et al., 2006). There is a high incidence (45%) of associated psychiatric disease; most commonly, this is bipolar illness and schizophrenia. Imaging studies have revealed that DGS patients exhibit an approximate 10% decrease in overall brain volume (Schaer et al., 2006), with a similar loss of hippocampal volume (Debbane et al., 2006; Deboer et al., 2007), reduction in cortical thickness, decreased cortical gyrification, and cerebellar hypoplasia. Simon and colleagues recently reported hypomorphic fronto-parietal cortical white matter tracts in a group of DGS patients that they associate with nonverbal cognitive impairment (Simon et al., 2008).

The ERK2 gene, *MAPK1,* is located on chromosome 22, at a position distal to the 3 Mb DGS region. A number of unrelated patients have been identified with deletions of this distal region of chromosome 22q11 that include the *MAPK1* gene, but which do not physically overlap the DGS deletion (Ben-Shachar et al., 2008; Rauch et al., 1999; Saitta et al., 1999). Importantly, patients with distal deletions independently exhibit a spectrum of craniofacial abnormalities, cardiac defects, and neurodevelopmental deficits. These findings suggest that haploinsufficiency for different elements of the MAPK cascade can result in similar anatomic and intellectual manifestations, implying sensitivity to dosage of various elements of the ERK signaling cascade.

In early 2008 there were two independent reports linking approximately 1% of all cases of autism with deletions or duplications of a 593 kb region on chromosome 16p11.2. This locus encompasses the *MAPK3* gene that encodes ERK1 (Kumar et al., 2008; Weiss et al., 2008). Remarkably, these individuals exhibited dysmorphic facial features and congenital heart defects that were noted to be similar to those observed in DGS (Ballif et al., 2007; Ghebranious et al., 2007). While autism is not a common feature of NCFC syndromes, there are reports of autism in DGS patients and in those with other syndromes.

Developmental Roles of the ERKs

The discovery of the linkage of the ERK pathway to a number of CNS syndromes in humans has served to refocus attention on the underlying actions of these molecules. Remarkably little is known about the biology of the ERKs in vivo, and indeed many assumptions about their roles have been contravened by new data from animals in which the ERKs have been knocked out. Given the importance of these enzymes, it was surprising that genetic inactivation of the ERK1 gene, *Mapk3*, did not result in an overt phenotype. Knockout of the ERK2 gene, *Mapk1*, however, resulted in early embryonic lethality, due principally to failed placental/trophoblast development (Aouadi et al., 2006). The recent generation of conditional ERK2 knockouts has provided new insight into the biology of these enzymes. One of the central unanswered questions in understanding the roles of the ERKs in CNS function is to what degree the functional impairments result from abnormalities in development or, alternatively, reflect an ongoing requirement for ERK activity in synaptic transmission, memory formation, and cognitive function.

Seminal studies in the mouse (Corson et al., 2003), chick (Lunn et al., 2007), *Xenopus* (Christen and Slack, 1999), and zebrafish (Shinya et al., 2001) reported the rather surprising finding that activated forms of ERK1/2 were spatially restricted to regions of the embryo that were developing under the influence of FGF, and that ERK activation could be blocked by pharmacological inhibition of FGFR function. Prominent regions that develop in response to FGF action include the branchial arches, migrating neural crest cells, the midbrain/hindbrain boundary, and developing forebrain (Figure 2). These observations appeared counterintuitive, based on a vast literature describing the broad actions of the ERKs in conveying signals from the majority of cell surface receptors. These data provided the first evidence that in vivo these enzymes might direct development in a highly selective manner within circumscribed populations of progenitors. The linkage of ERK activation to FGF signaling has proven to be a key finding in explaining their developmental roles.

A prominent feature of human syndromes related to mutations in ERK signaling pathways is the coincidence of CNS, cardiac, and craniofacial phenotypes. This coincidence arises from the fact that a subset of neuroepithelial derivatives that are targets of ERK signaling, neural crest cells, contribute not only to development of the nervous system, but to morphogenesis of the heart, cranium, and face (Figure 2).

ERK1/2 in Neural Crest Development

Gail Martin and colleagues demonstrated the essential actions of the FGFs in development through genetic regulation of FGF8 expression within the neural crest and neural tube (Meyers et al., 1998; Storm et al., 2006). Reduction in FGF8 levels resulted in the failure to generate a normal complement of neural crest cells, leading to severe cardiac and craniofacial defects (Meyers et al., 1998). The phenotypic severity was directly related to the levels of FGF8. Importantly, disruption of FGF8 expression in the developing neural tube dramatically affected normal CNS patterning, leading to the failure to develop a cerebellum, olfactory bulb, and a normal cerebral cortex (Chi et al., 2003). These morphogenetic events have subsequently been shown to be reliant upon ERK signaling (Kawauchi et al., 2005). Recently, Newbern and colleagues have reported that genetic inactivation of ERK2 in the developing neural crest results in cardiac abnormalities and craniofacial defects similar to those observed in the FGF8 hypomorphs and analogous to phenotypes observed in humans haploinsufficient for the *MAPK1* gene encoding ERK2 (Newbern et al., 2008). Mice in which both ERK isoforms were inactivated in the developing neural crest displayed a more severe phenotype. Significantly, similar phenotypes were observed upon conditional knockout of upstream elements of the ERK cascade, B-Raf/Raf1 and MEK1/2, as well as knockout of the transcription factor SRF, which is a direct downstream target of ERK signaling (Newbern et al., 2008). These data provide clear evidence that signaling through the ERK cascade is essential for normal neural crest development.

ERK1/2 in Cortical Development

The actions of the ERKs in the developing brain have only recently been examined and have revealed a critical role for ERK2 in cortical development. The first study in which ERK2 was conditionally knocked out of the developing brain has provided new insight into the biological actions of this enzyme. Inactivation of ERK2 within cortical neural progenitor cells early in the neurogenic period results in a thinner, but normally organized, cortex. The ERK2-deficient mutant cortex contains fewer neurons but many more astrocytes (Samuels et al., 2008). The neuronal loss was the result of selective suppression of division intermediate progenitor cells. The intermediate progenitor cells are a recently recognized subclass of neural progenitors positioned within the subventricular zone that undergo symmetric terminal divisions to generate neurons that then populate all layers of the developing cortex (Pontious et al., 2008). Previous work had documented a clear requirement for ERK activity in FGF-stimulated cortical progenitor differentiation and neurogenesis (Menard et al., 2002). The cortical phenotypes in the ERK2 conditional knockout mice are consistent with the action of the ERKs in conveying FGF signals. FGFs play critical roles in cortical development and there is good evidence demonstrating ERK activity as a primary effector of growth factor action. Reduction of FGF8 expression suppresses neural progenitor proliferation and increases cell death, resulting in abnormal cortical structure and patterning (Meyers et al., 1998; Storm et al., 2006). Similarly, FGF2 null animals exhibit impaired neural progenitor proliferation, resulting in a 40% reduction in cortical neurons in the mature frontal and parietal cortex (Zheng et al., 2004). Analogous phenotypes are observed upon inactivation of FGFRs (Shin et al., 2004). Conversely, exogenous application of FGF2 (Vaccarino et al., 1999) or expression of a constitutively active FGFR3 (Inglis-Broadgate et al., 2005) resulted in increased numbers of neurons and cortical volume due to stimulation of neural progenitor proliferation as a direct result of enhanced ERK signaling (Thomson et al., 2007).

Compelling evidence supporting a role for the ERKs in cortical neural progenitor proliferation and differentiation has come from analyzing the effects of mutations of the scaffolding molecules FRS2 and SHP2 (Figure 1). FRS2 is an essential adaptor protein linking both the FGFRs and Trks to activation of the ERKs. This linkage is achieved

through receptor-dependent phosphorylation of FRS2 that allows the formation of a signaling complex with SHP2 that is necessary for ERK pathway activation (Hadari et al., 2001). Mice that express mutant forms of FRS2 exhibit smaller brains, with an approximate 30% reduction in cortical thickness and fewer neurons (Yamamoto et al., 2005). This effect was shown to be a consequence of dramatically reduced levels of ERK activation, specifically resulting in reduced numbers of proliferating intermediate progenitor cells in the subventricular zone. These cells have recently entered the spotlight as they are believed to underlie the evolutionary expansion in size and the increased surface area and gyrification of the cortex (Pontious et al., 2008). The mutant FRS2 phenotype is very similar to that observed in mice in which ERK2 was conditionally inactivated during cortical neurogenesis (Samuels et al., 2008). Significantly, Freda Miller's lab has recently shown that deletion or inactivation of the adaptor molecule SHP2, which is mutated in Noonan and LEOPARD syndromes, in cortical progenitors was found to inhibit neurogenesis and promote precocious astrocyte generation through ERK-dependent mechanisms (Gauthier et al., 2007). Conversely, SHP2 gain-of-function mutations led to generation of supernumerary neurons and inhibition of gliogenesis. Conditional inactivation of B-Raf in neural progenitors resulted in reduced cortical thickness in the postnatal brain (Zhong et al., 2007) and hypomyelination (Galabova-Kovacs et al., 2008) phenotypes, which were both associated with reduced ERK activation.

ERKs in Cellular Survival

It has been widely accepted that the ERKs play essential roles in neuronal survival, owing to seminal studies by Greenberg and colleagues (Xia et al., 1995) that were subsequently verified by many other reports using in vitro models. Recent in vivo studies examining the effect of genetic inactivation of the ERKs or their upstream regulators have shown conflicting data. Conditional inactivation of ERK2 in the developing cortex did not result in apoptotic neuronal death (Samuels et al., 2008), nor was cell death observed in mice in which both ERK isoforms were inactivated (I.S.S. and G.E.L., unpublished data). These findings are consistent with studies of cortical development by Miller and colleagues in which MEK (Paquin et al., 2005) and SHP2 (Gauthier et al., 2007) are inactivated in cortical progenitor cells in vivo. The loss of either protein results in reduced ERK activity within these cells and causes them to remain undifferentiated until gliogenic stimuli induce them to differentiate into astrocytes. The resultant cortices are composed of reduced numbers of neurons due to altered fate of the progenitors, thereby defining a role for the ERKs in neuronal differentiation and cell fate determination rather than survival of these cells (Gauthier et al., 2007; Paquin et al., 2005). Similarly, conditional knockout of Raf1 and B-Raf resulted in the loss of ERK signaling leading to reduced neurogenesis (Zhong et al., 2007) and dysmyelination (Galabova-Kovacs et al., 2008), secondary to impaired progenitor proliferation, but not apoptosis. Consistent with these findings, inactivation of both ERK isoforms in B-lymphocyte lineages was associated with reduced proliferation, but not apoptosis (Yasuda et al., 2008). Thus far, studies in vivo have not supported an obligatory role for the ERKs in cellular survival.

ERKs in Memory and Learning

The ERKs are potently activated by synaptic activity, and they are essential for synaptic plasticity related to learning and memory formation in mammals and invertebrates (Davis and Laroche, 2006). Activation of neurotransmitter receptors results in the initiation of both calcium-dependent and -independent signaling mechanisms that serve to activate the Ras-related small GTPases (Thomas and Huganir, 2004). Early work by Sweatt and colleagues demonstrated an absolute requirement for ERK activity in induction of LTP (English and Sweatt, 1996), and subsequent studies have established its necessity for NMDA-dependent

and -independent forms of LTP induction and maintenance. The molecular basis of these effects is the subject of intense interest and a number of mechanisms have been investigated including ERK-dependent regulation of AMPA receptor insertion into the postsynaptic membrane, physical remodeling and generation of dendritic spines, Kv4.2 potassium channel function, and the local regulation of protein synthesis (Thomas and Huganir, 2004). Significantly, the Svoboda lab recently reported that glutamate stimulation of a single dendritic spine resulted in sustained alteration of the volume of the stimulated spine and subsequent enlargement of neighboring spines that was reliant upon ERK activation, arguing that such mechanisms underlie the development of LTP (Harvey et al., 2008). The ERKs also have newly appreciated roles in memory consolidation. It was recently reported that in the hippocampus there is circadian oscillation of ERK activation that is essential for persistent and stable memory formation (Eckel-Mahan et al., 2008), documenting another unexpected level of complexity in the actions of the ERKs in memory.

New mouse models targeting the ERKs themselves have provided additional direct evidence of their involvement in learning and memory. Previous behavioral analysis of mice treated with inhibitors of ERK activity demonstrated the importance of ERK signaling in a broad range of memory and learning tasks (Davis and Laroche, 2006). Thus, it was quite surprising that analysis of ERK1 knockout mice revealed only a rather subtle behavioral phenotype (Mazzucchelli et al., 2002; Selcher et al., 2001). Genetic inactivation of the ERK1 gene results in hyperactivity (Selcher et al., 2001), and the animals exhibit a generalized behavioral excitement phenotype with altered responses to amphetamine (Engel et al., 2008) and cocaine (Ferguson et al., 2006; Grueter et al., 2006). ERK1 knockout mice have recently been used as models for mania and bipolar disorder (Engel et al., 2008). ERK1 null mice are also reported to have a paradoxical improvement in a striatal-based long-term memory task and facilitation of LTP in the nucleus accumbens (Mazzucchelli et al., 2002) that was argued to result from compensatory actions of ERK2. The recently recognized genetic linkage of ERK1 to autism suggests that a more extensive behavioral analysis of these animals is in order.

The recent development of conditional ERK2 alleles (Samuels et al., 2008) and ERK2 hypomorphic mice (Satoh et al., 2007) has shed new light on the roles of ERK2 in memory and learning. Samuels and colleagues reported that mice in which ERK2 was knocked out in telencephalic radial glial progenitors exhibit profound deficits in associative learning in a fear conditioning assay (Samuels et al., 2008). Satoh et al. generated ERK2 hypomorphic mice that exhibit an approximate 30% reduction in ERK2 levels and an overtly normal brain (Satoh et al., 2007). Strikingly, these mice exhibit impairment in fear conditioning and deficits in two spatial memory tasks. These data suggest that even modest reduction of ERK2 function is sufficient to result in behavioral impairment. The interpretation of the behavioral phenotypes in hypomorphs, or mice in which the ERKs are inactivated during development, raises the question of whether the deficiencies arise from developmental-related structural perturbations of the brain or are reflective of the acute actions of these enzymes in synaptic function and plasticity. Analysis of mice in which ERK2 has been conditionally inactivated at later developmental times will likely provide insight into the relative actions of ERK2, and these studies are currently underway in several laboratories.

Summary

Taken together these findings argue that mammalian development is exquisitely sensitive to perturbations in signaling through the ERK pathway, and either gain of function or loss of function of a single allele of an ERK pathway gene is sufficient to result in abnormal brain development and function. The recognition that the ERKs play very specific roles in CNS development that are linked to FGF signaling events, and are inexplicably restricted to

distinct populations of neural progenitors, has elucidated the novel actions of these enzymes in the morphogenesis and plasticity of the brain. Collectively, these studies underscore our primitive understanding of the biology of the ERK signaling pathway in vivo and its unexpected complexity.

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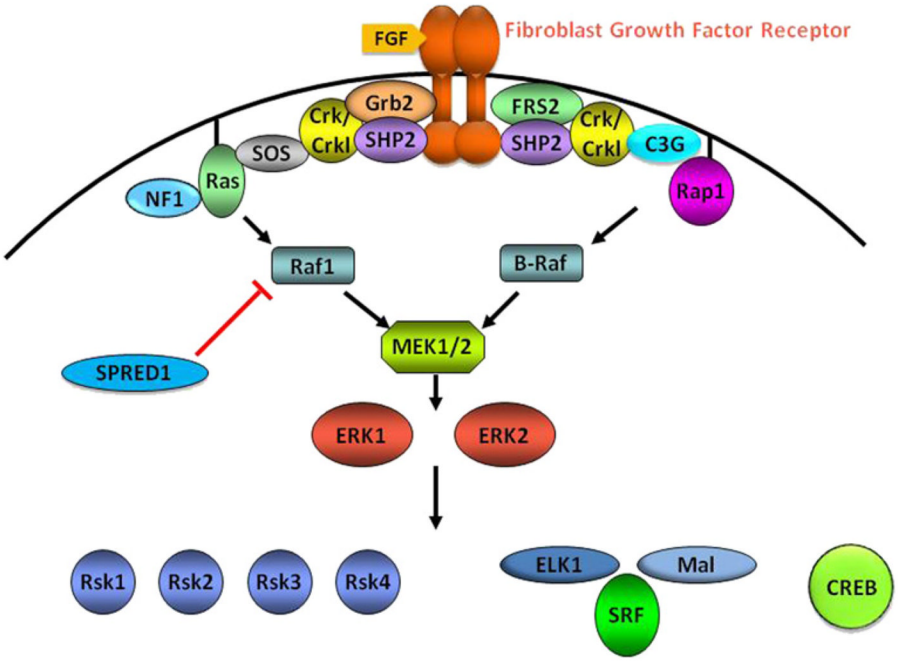

Figure 1.
The ERK Signaling Cascade

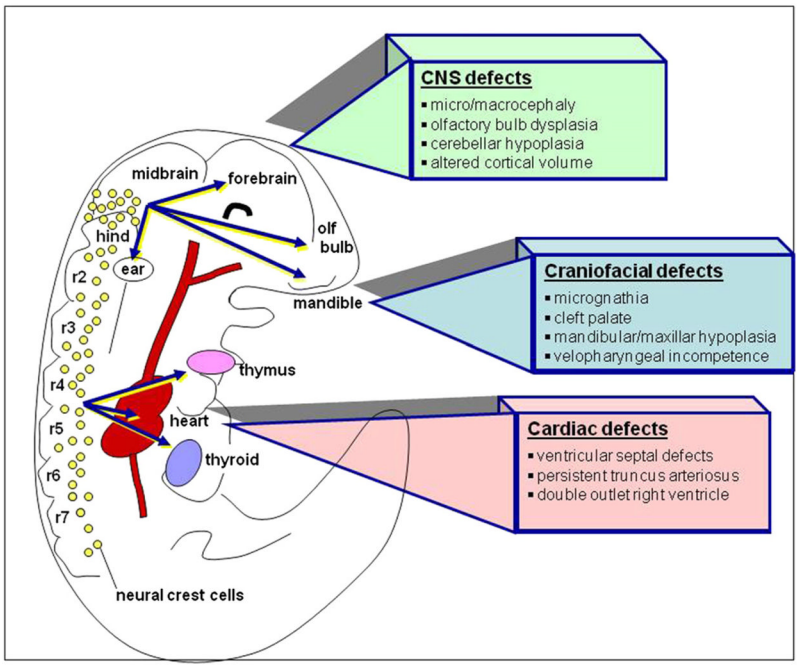

Figure 2.
ERK Activity Is Necessary for the Normal Development of Neural Crest and the Central Nervous System

Table 1

Developmental Disorders with Altered ERK Pathway Signaling

Syndrome	Mutated Gene	ERK Signaling (Gain/Loss of Function)	Intellectual Impairment
Costello	H-RAS	+	moderate
Cardio-facio-cutaneous	K-RAS	+	moderate-severe
	B-RAF	+ and −	moderate-severe
	MEK1	+	moderate-severe
	MEK2	+	moderate-severe
Noonan	PTPN11/ SHP2	+	variable
	K-RAS	+	variable
	SOS1	+	variable
LEOPARD	PTPN11/ SHP2	−	normal-mild
	RAF1	+	normal-mild
DiGeorge/22q11 deletion	TBX1−→FGF8	−	mild-moderate
	CRKL	−	mild-moderate
Distal 22q11 deletion	ERK2	−	mild-moderate
Neurofibromatosis type 1	NF1 (mut)	+	normal-moderate
	NF1 (del)	+	moderate
NF1-like syndrome	SPRED1	+	mild
Autism (del/ dup 16p11.2)	ERK1	+ and −	variable
Coffin-Lowry	RSK2	(−)	severe
X-linked mental retardation	RSK4	(−)	severe